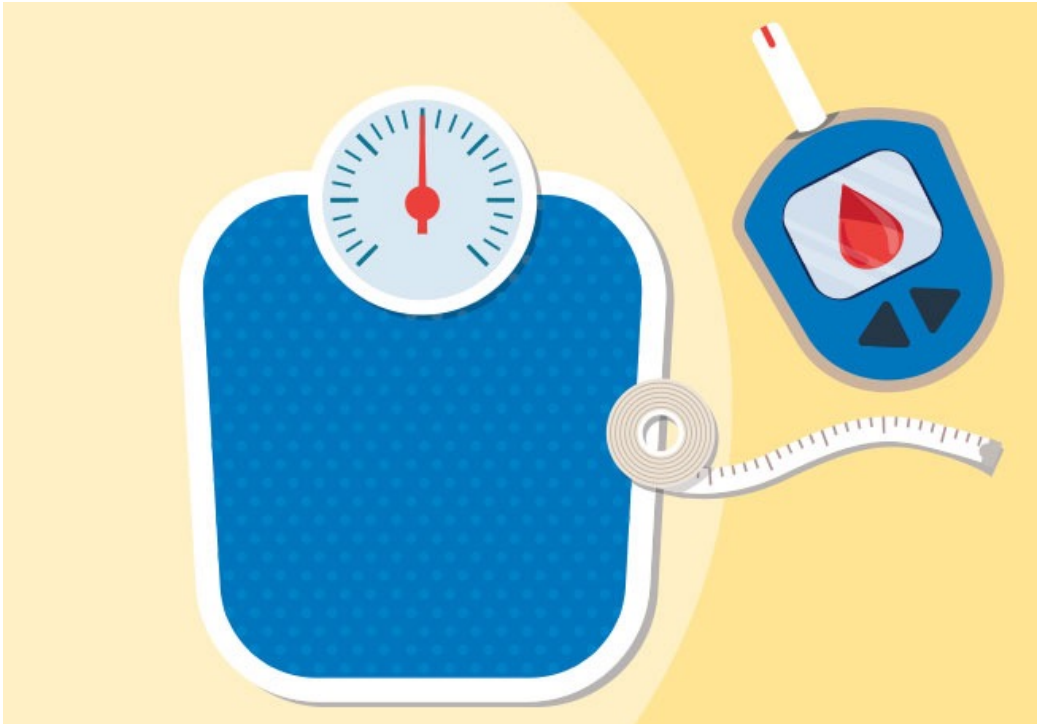
DALLAS OBESITY SOCIETY

To Engage, Educate, and Empower Obesity Treatment in Dallas-Fort Worth

Obesity as a Treatment Target in Type 2 Diabetes



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UT Southwestern, Dallas, Texas, USA

UT Southwestern
Weight Wellness

Disclosures

Consultant/Advisory Boards: Novo Nordisk, Boehringer Ingelheim, and Eli Lilly and Company

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Case Discussion

Linda Jones
62-year-old accountant recently discharged following NSTEMI and 3 stents to LAD. BMI 42, BP 138/88, HR 64

PMHx
T2D x 9 years (A1c 9.8%), HTN, MAFLD, HLD

Current Meds
Metformin 1000 mg twice daily
Glimepiride 4 mg daily
70/30 Insulin 15 units twice daily *started in hospital
Rosuvastatin 5 -> 20 mg daily
Metoprolol 25 mg twice daily
Losartan 100 mg daily
Clopidogrel 75 mg daily

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OBJECTIVES

Outline the connection between type 2 diabetes (T2D) and obesity

Discuss the role of bariatric surgery and bariatric range weight reduction for treating T2D

Review emerging T2D and obesity medications that result in significant weight reduction

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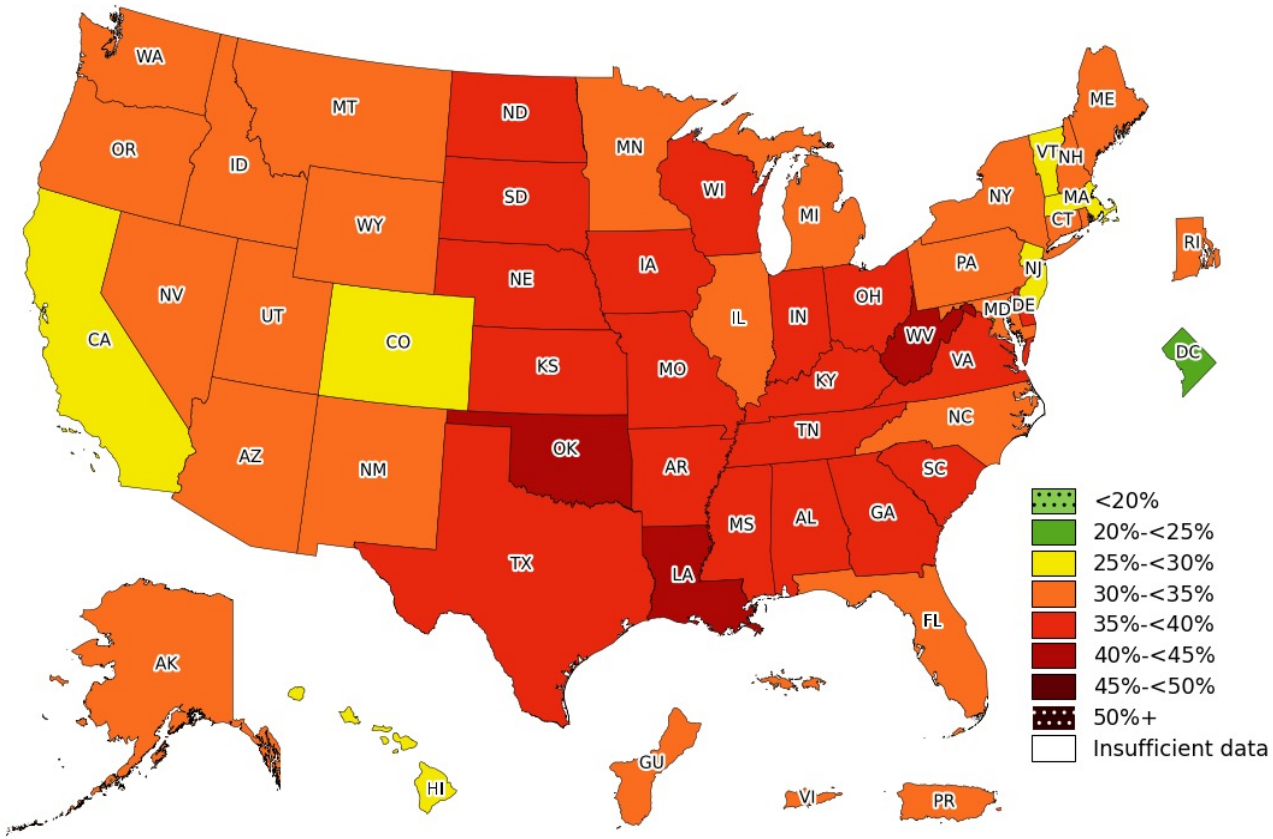
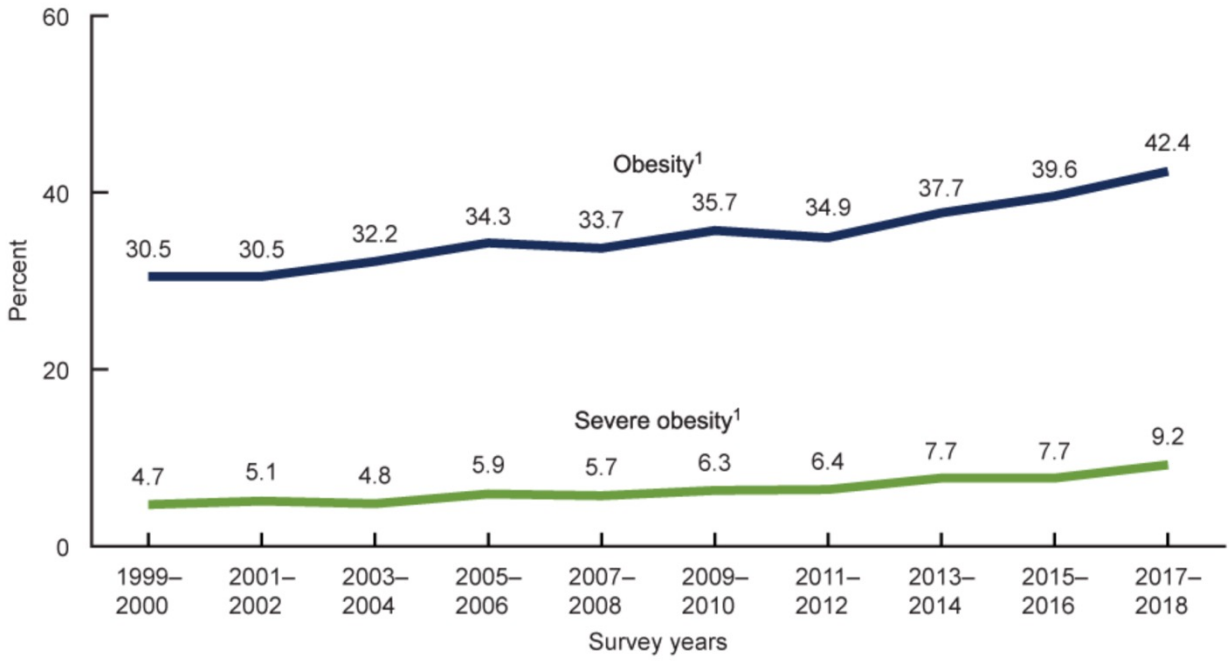
US Obesity Epidemic Grows

Native American, Non-Hispanic Black and Hispanic Groups most affected



Adult Obesity Prevalence Maps. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition, Physical Activity, and Obesity. (21 September 2023).

Trends in US Adults with Obesity 2000-2018

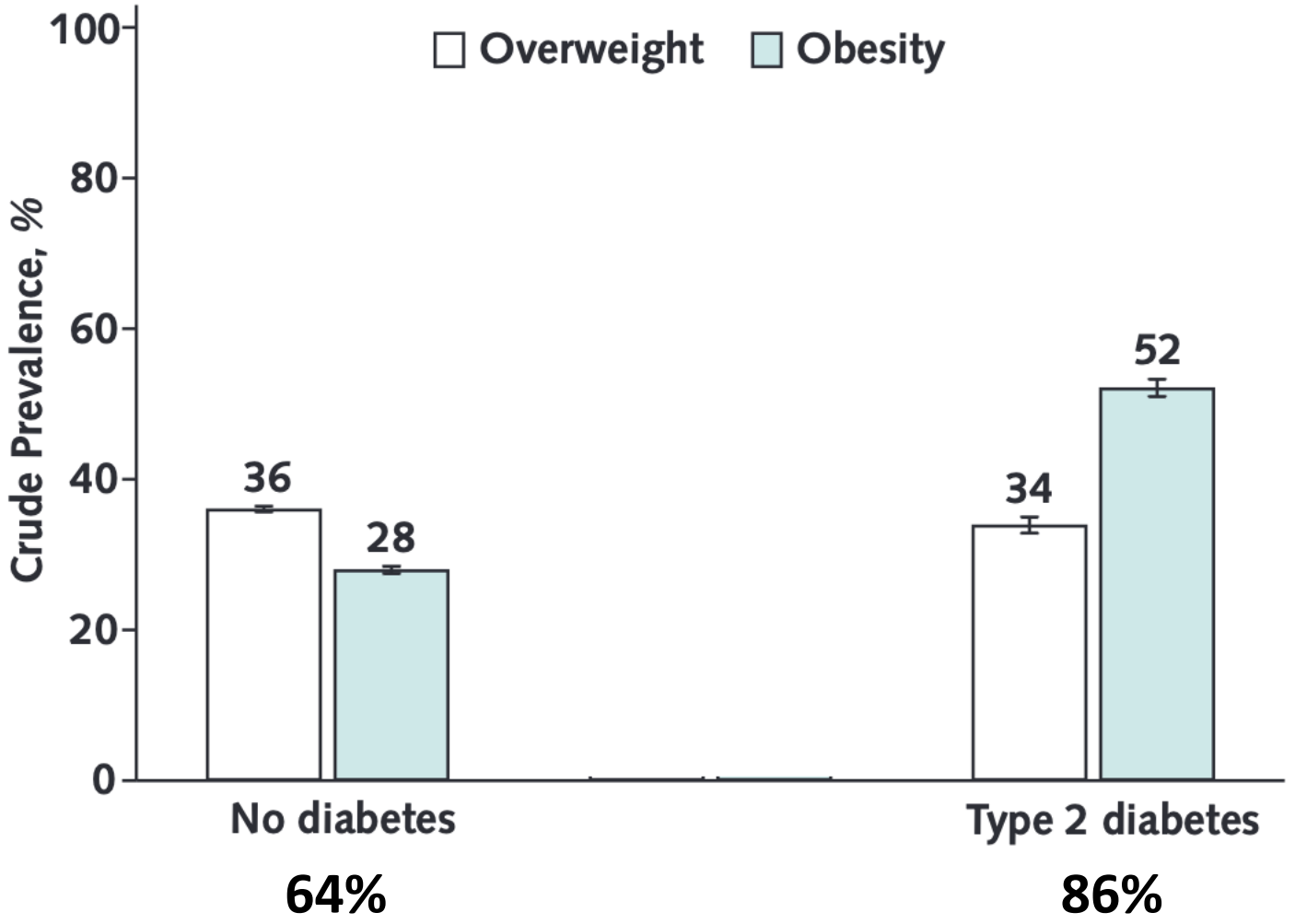


Obesity increased 30.5% to 42.4%

Severe obesity increased 4.7% to 9.2%

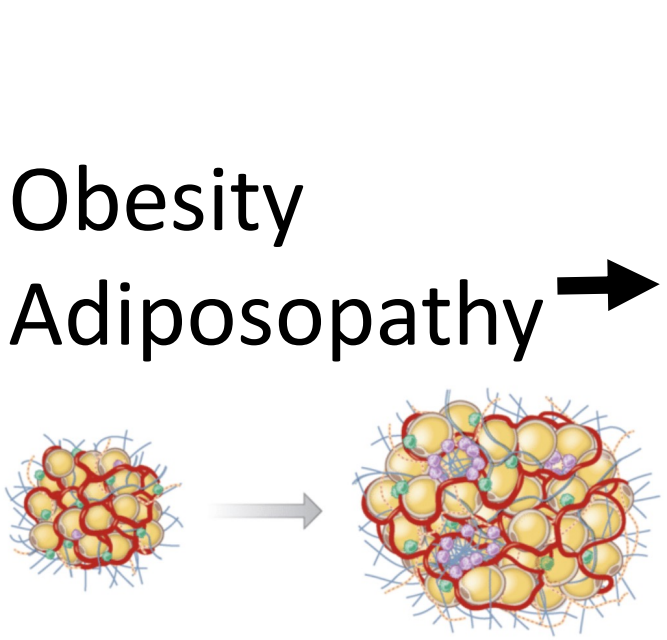
https://www.cdc.gov/nchs/data/databriefs/db360_tables-508.pdf#4

Prevalence of overweight and obesity in US adults by diabetes status: NHIS, 2016 to 2020



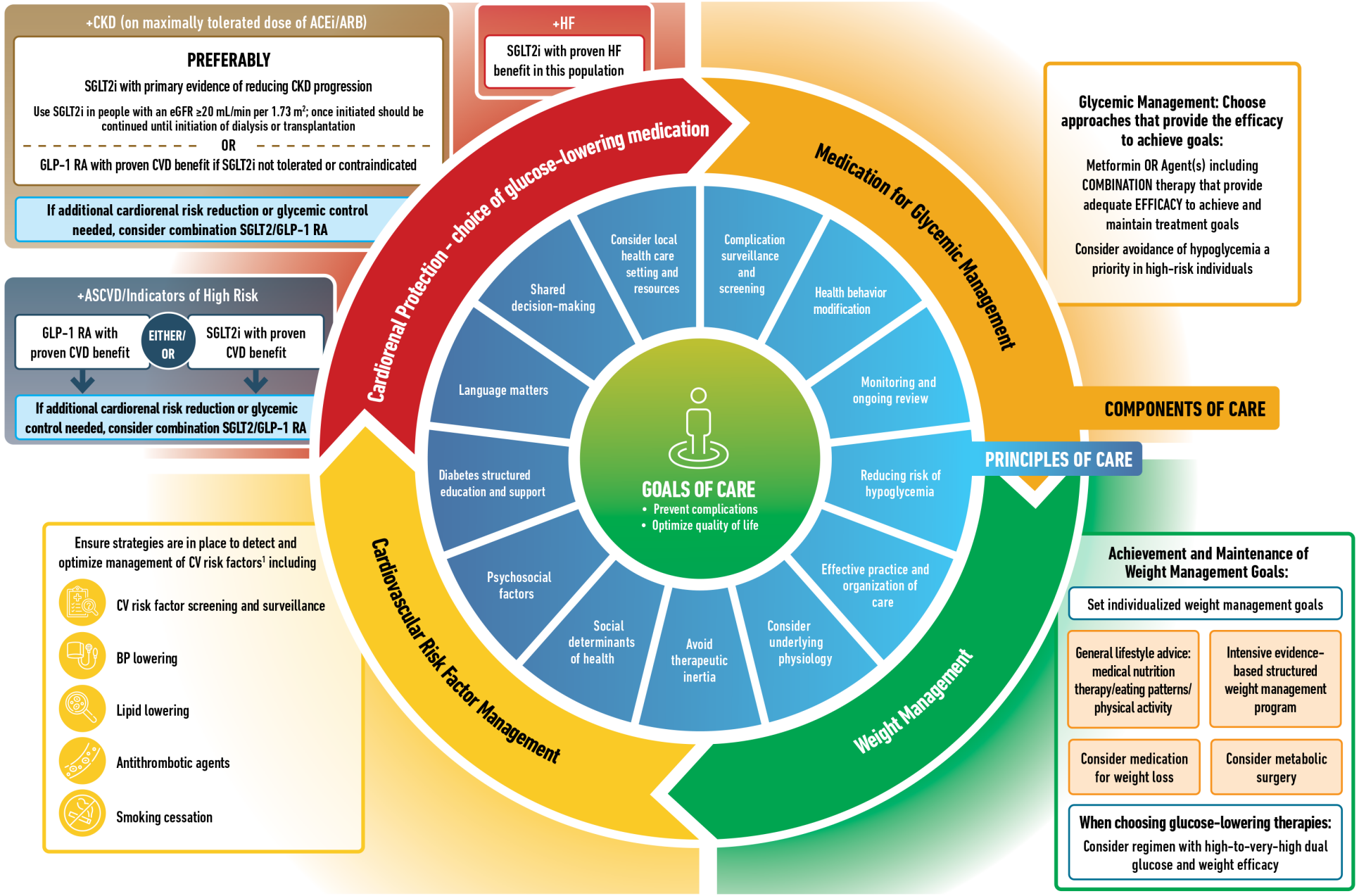
Fang M et al. Ann Intern Med. 2023 Mar;176(3):427-429

Treating Adiposity or Its Downstream Complications



Lingvay et al. Lancet 2022; 399: 394–405

HOLISTIC PERSON-CENTERED APPROACH TO T2DM MANAGEMENT



American Diabetes Association®

Davies M et al. Diabetes Care. 2022;45(11):2753-2786

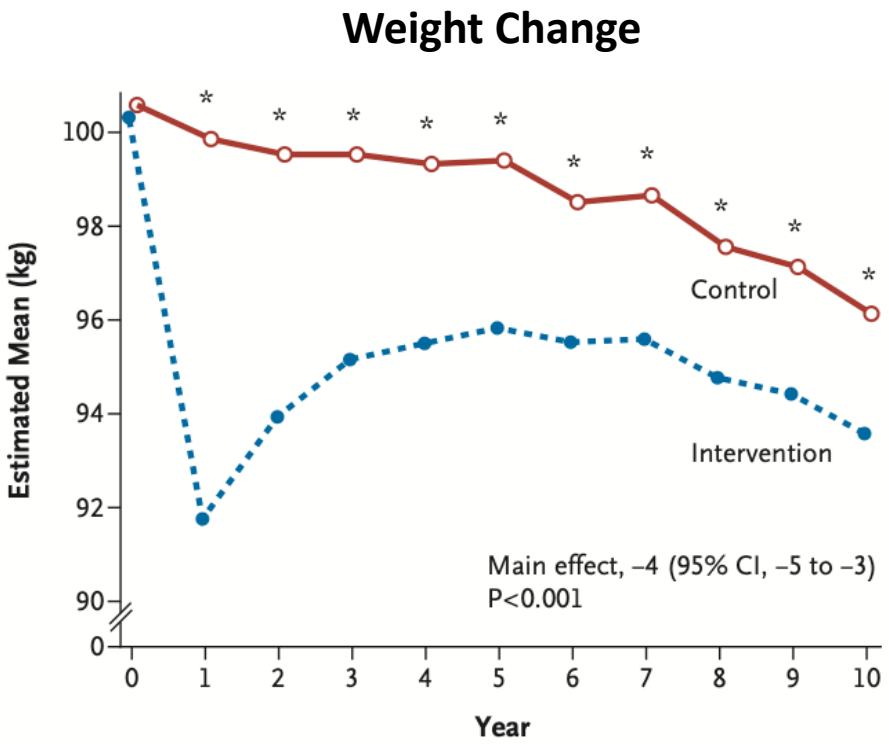
Weight Loss in T2D and CV Events Reduction

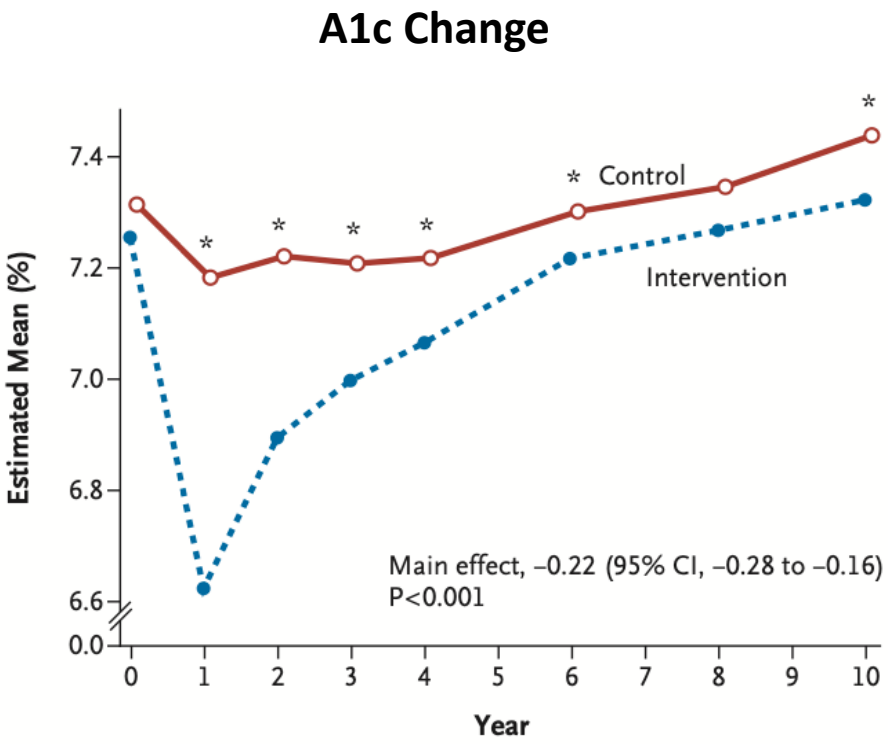
Look AHEAD

Weight loss of 8.6% at 1 yr
No reduction CV death, MACE

Post-hoc Analysis

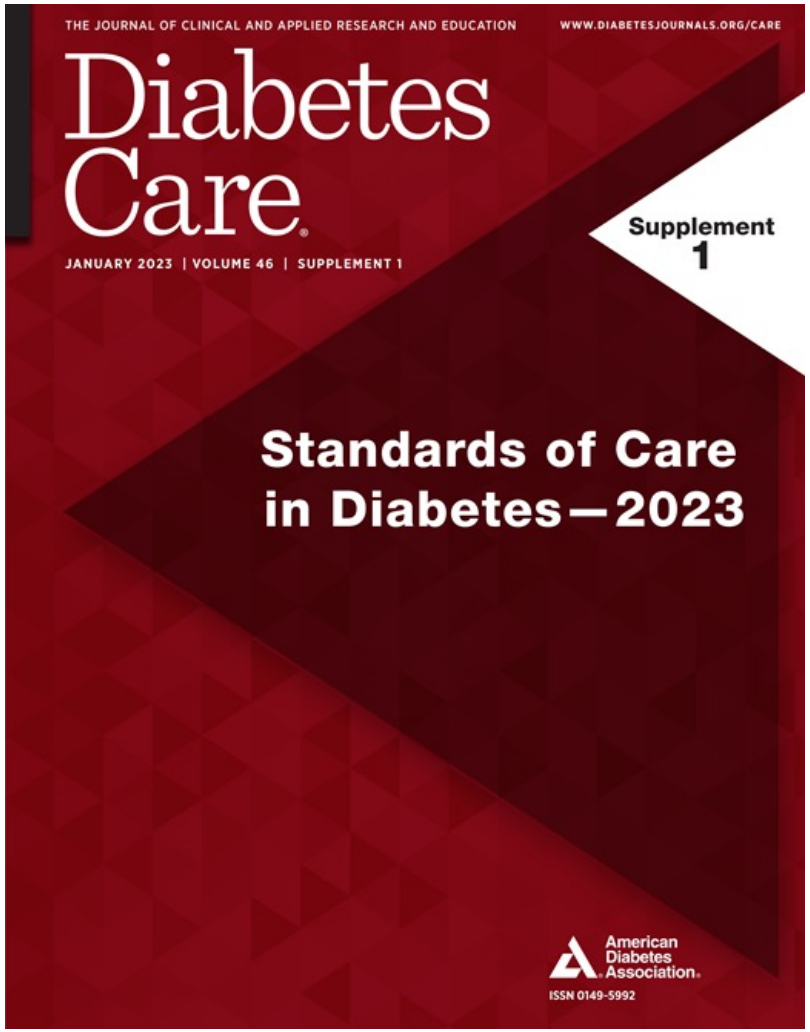
Those with ≥10% weight loss
- 20% lower CV mortality
- 21% lower MACE





NEJM 2013;369:145-54, Lancet Diabetes Endocrinol 2016; 4: 913–21

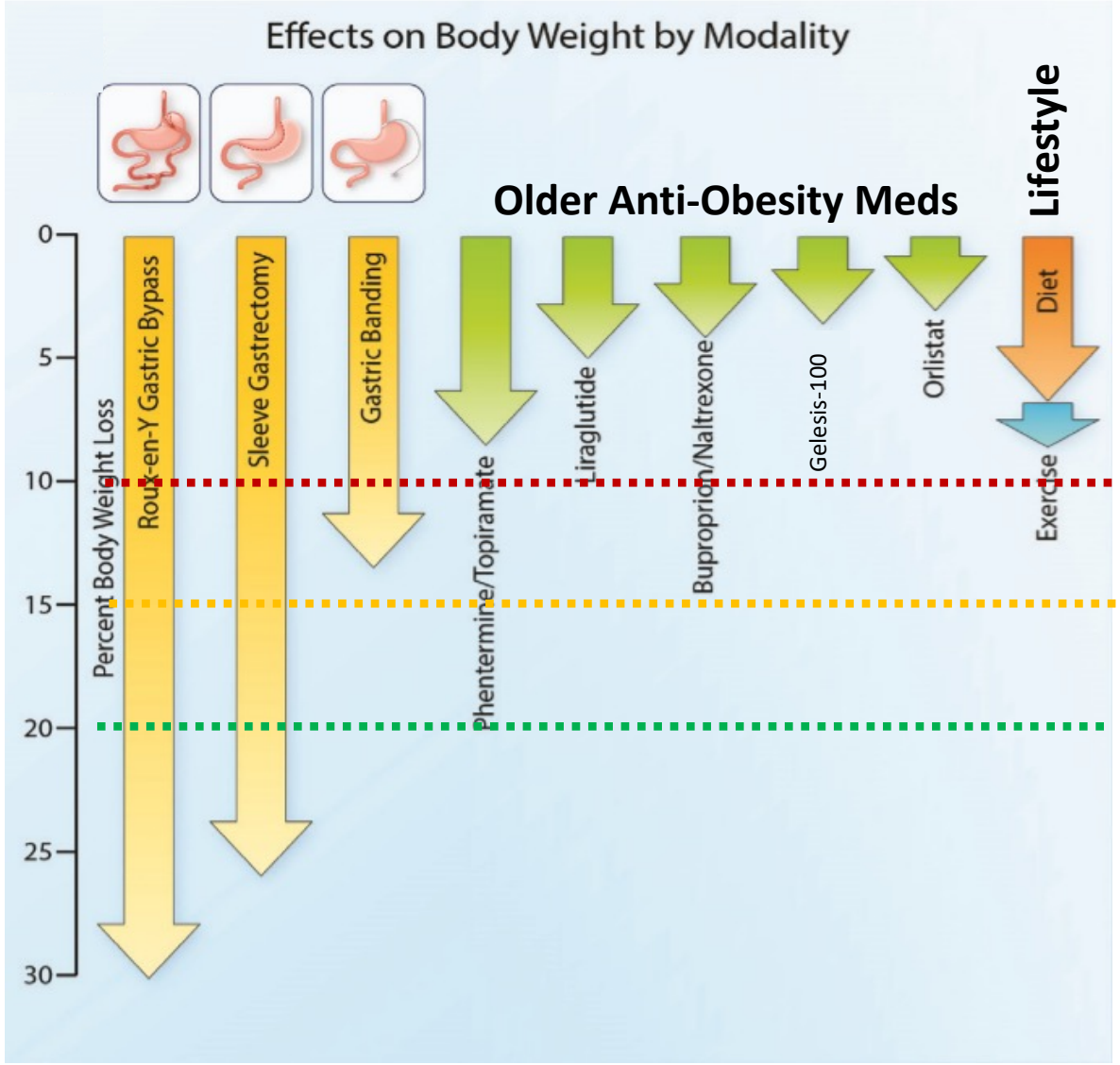
Focus on Obesity



8.5 Individuals with diabetes and overweight or obesity may benefit from modest or larger magnitudes of weight loss. Relatively small weight loss (approximately 3–7% of baseline weight) improves glycemia and other intermediate cardiovascular risk factors. **A** Larger, sustained weight losses (>10%) usually confer greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and may improve long-term cardiovascular outcomes and mortality. **B**

ElSayed NA, *et al*. Diabetes Care. 2023;46:S128–39.

Clinically Significant Weight Reduction is not Easy



Circulation Research. 2020;126:1646–1665

Bariatric Surgery Criteria and Weight Reduction

Bariatric Surgery BMI Criteria

NIH Consensus Statement

BMI <35

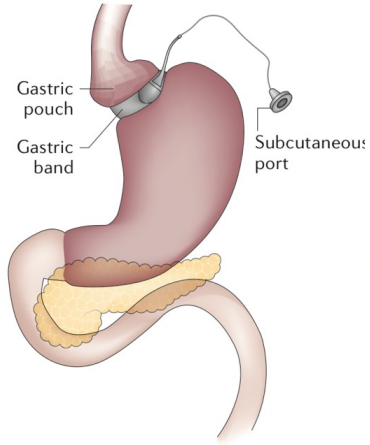
BMI 35-39
+ 1 comorbidity

+

BMI >40

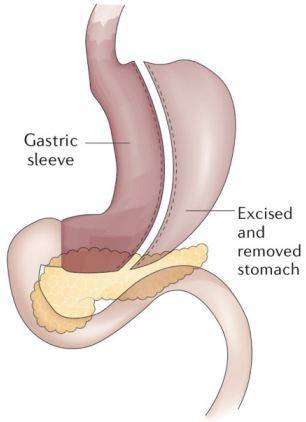
Comorbidities
Type 2 diabetes
Obstructive Sleep apnea
Hypertension
Atherosclerotic disease
Hyperlipidemia
Fatty liver disease

Adjustable Gastric Banding



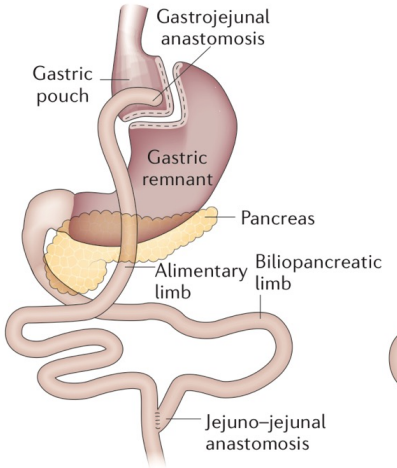
15%¶

Sleeve Gastrectomy



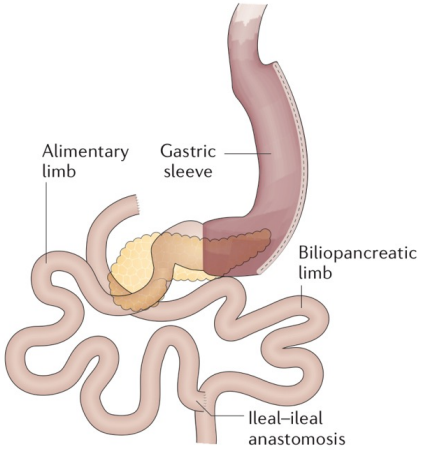
21.1%§

Roux-en-Y Gastric Bypass



24.5%§

Biliopancreatic Diversion w/ Duodenal Switch



33.82%ϟ

Weight Loss Outcomes

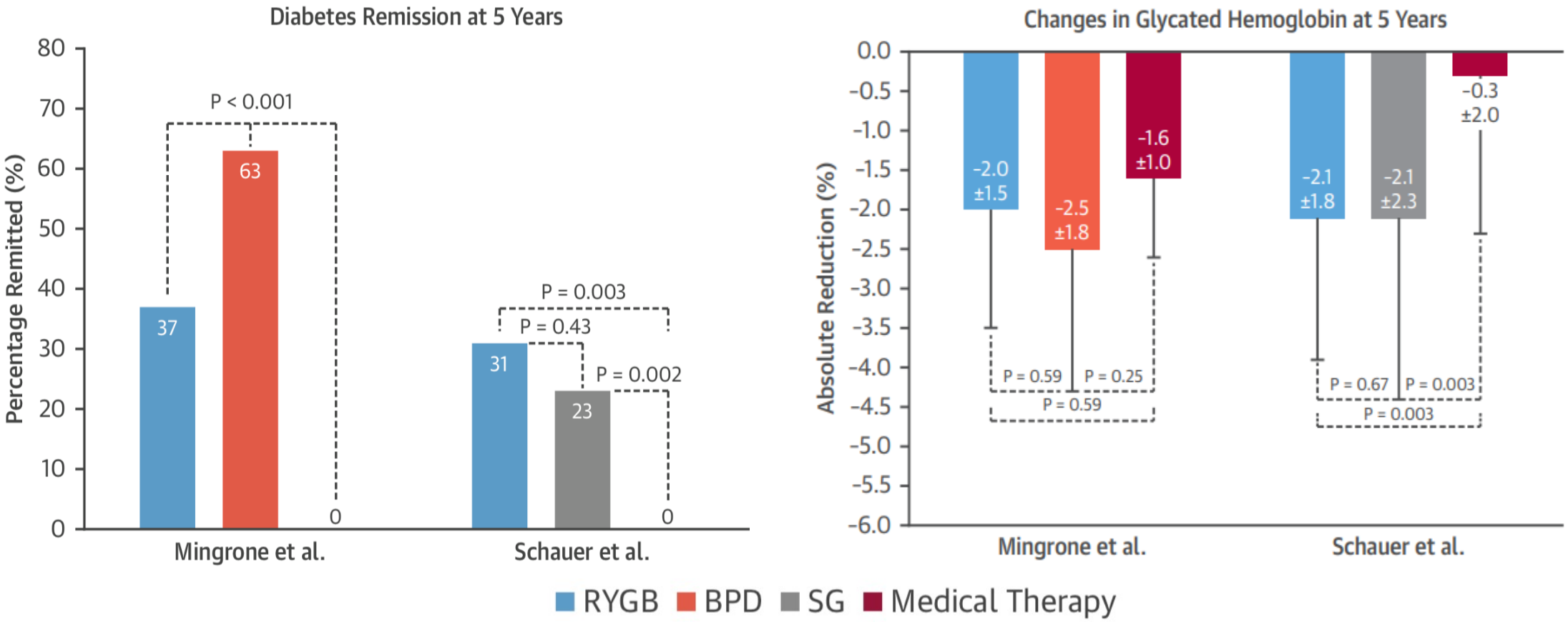
Ann Intern Med 1991;115:956-961

ϟN Engl J Med 2012;366:1577-85

§N Engl J Med 2014;370:2002-13

¶JAMA Surg. 2015;150(10):931-940

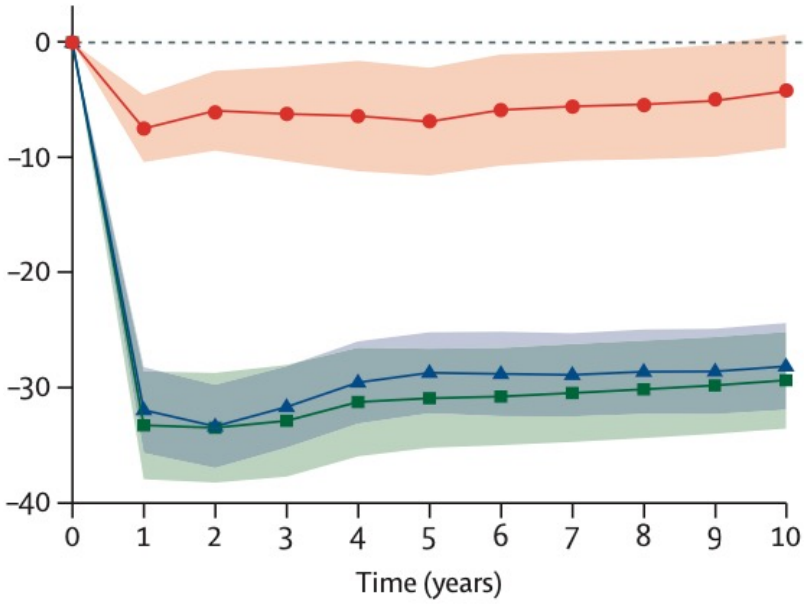
T2D Remission and A1c at 5 years Post-MBS



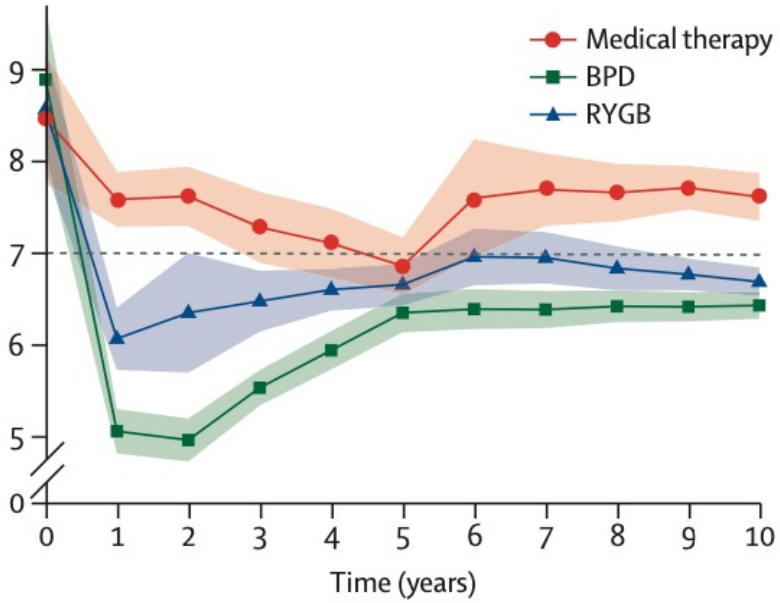
J Am Coll Cardiol. 2018, 13;71(6):670-687

T2D Complications 10 years Post-RYGB, BPD

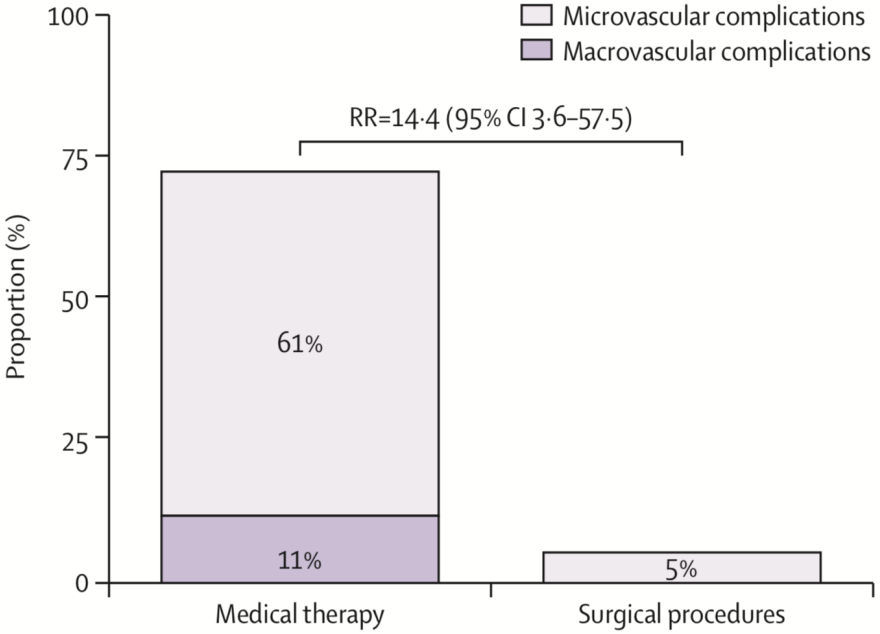
Weight Change



A1c Change



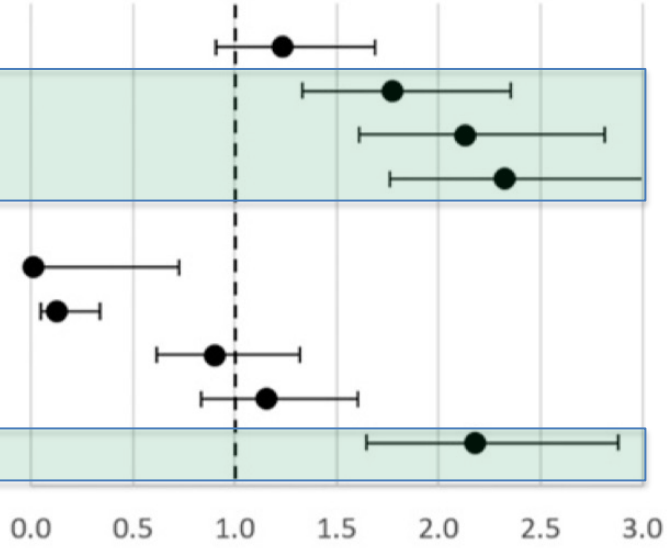
T2D Complications at 10 Years



Mingrone G et al. Lancet 2021; 397: 293–304

Predictors of T2D Remission after MBS

Weight loss	N	HR	p	CI
		No insulin use		
0-5%	73	Reference		
5-10%	236	1.23	0.19	(0.90 - 1.69)
10-15%	489	1.77	0.00	(1.33 - 2.36)
15-20%	822	2.13	0.00	(1.61 - 2.82)
> 20%	2326	2.32	0.00	(1.76 - 3.06)
		Insulin use		
0-5%	42	0.01	0.03	(0.00 - 0.73)
5-10%	120	0.12	0.00	(0.05 - 0.33)
10-15%	195	0.90	0.58	(0.61 - 1.32)
15-20%	335	1.16	0.38	(0.84 - 1.60)
> 20%	1290	2.18	0.00	(1.64 - 2.88)



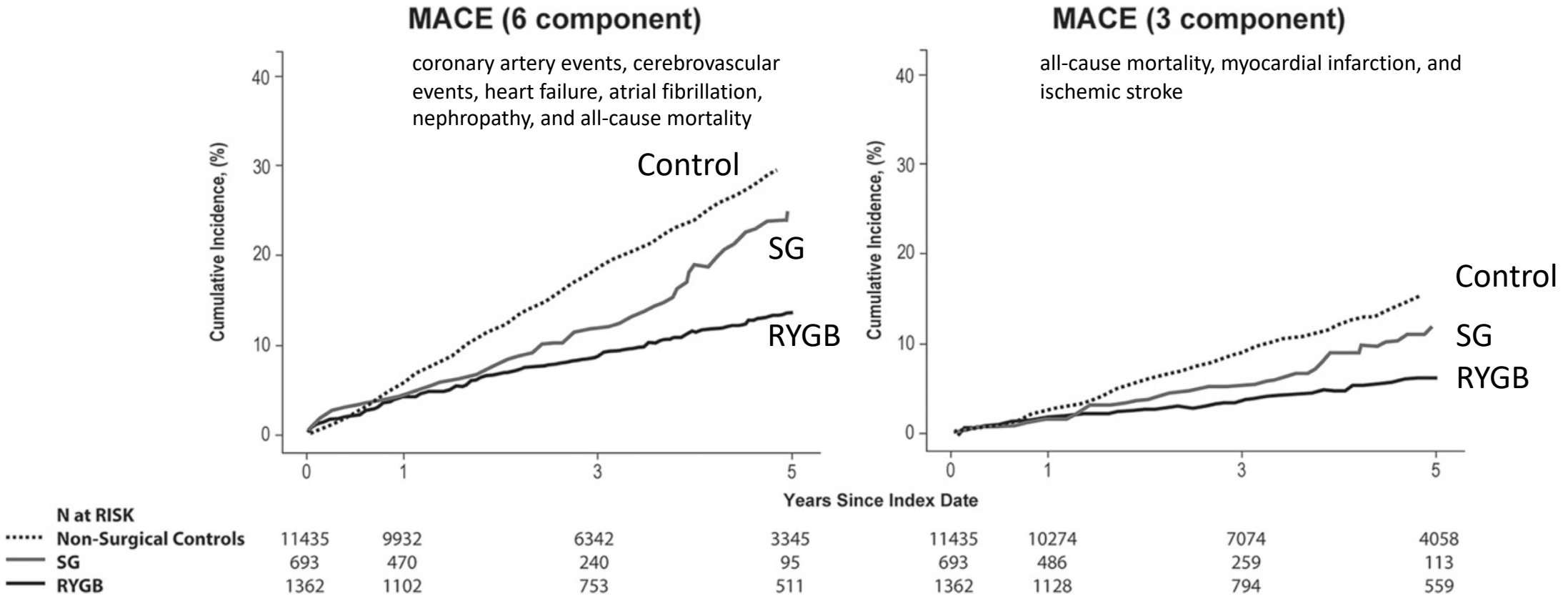
T2DM Remission Predictors

- Weight loss
- Shorter T2DM duration
- Good pre-op control
- Not on insulin
- Younger age
- Smaller waist circumference
- Presence of NAFLD

JAMA. 2014;311(22):2297-2304
J Am Coll Cardiol. 2018; 13;71(6):670-687
Diabetes Care. 2021; 44(2): 321–325
Diabetes Care 2022;45(1):92–99

Cardiovascular Outcomes in Type 2 Diabetes

Comparison of Gastric Bypass, Sleeve Gastrectomy, and Usual Care

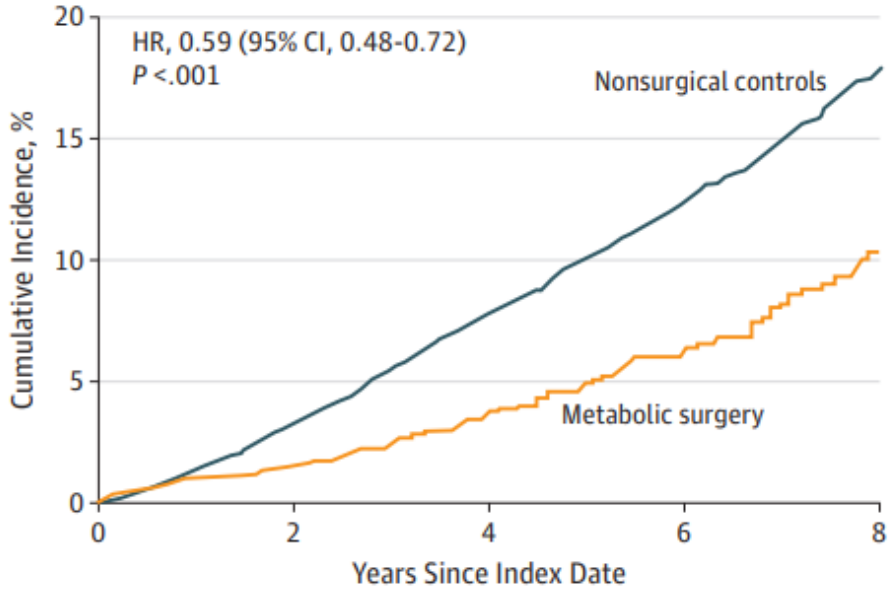


RYGB may be associated with greater weight loss, better glycemic control, and lower risk of MACE and nephropathy vs. sleeve gastrectomy

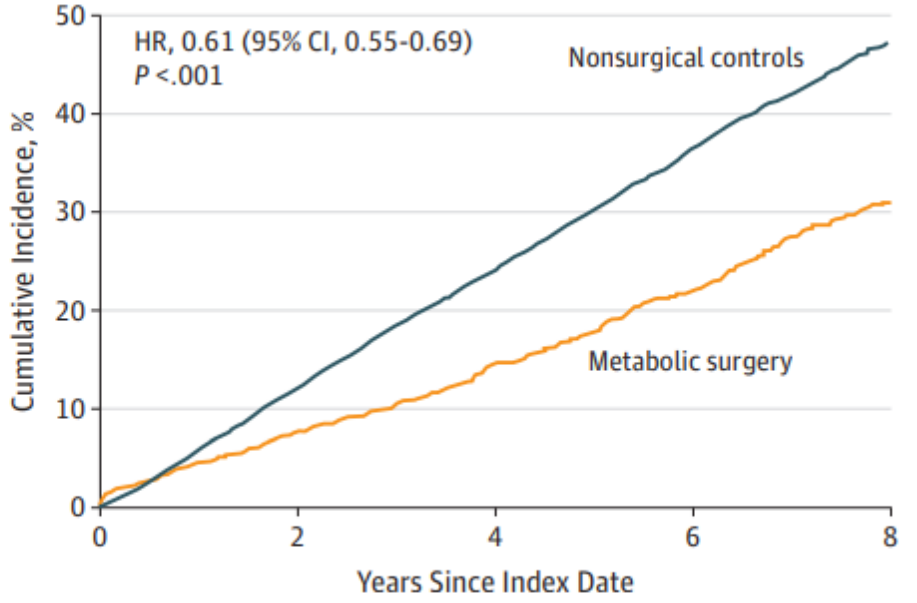
Diabetes Care 2021;44:2552–2563

Bariatric Surgery in T2D - Associated with Lower Mortality and MACE

All-Cause Mortality



Primary MACE Composite Outcome

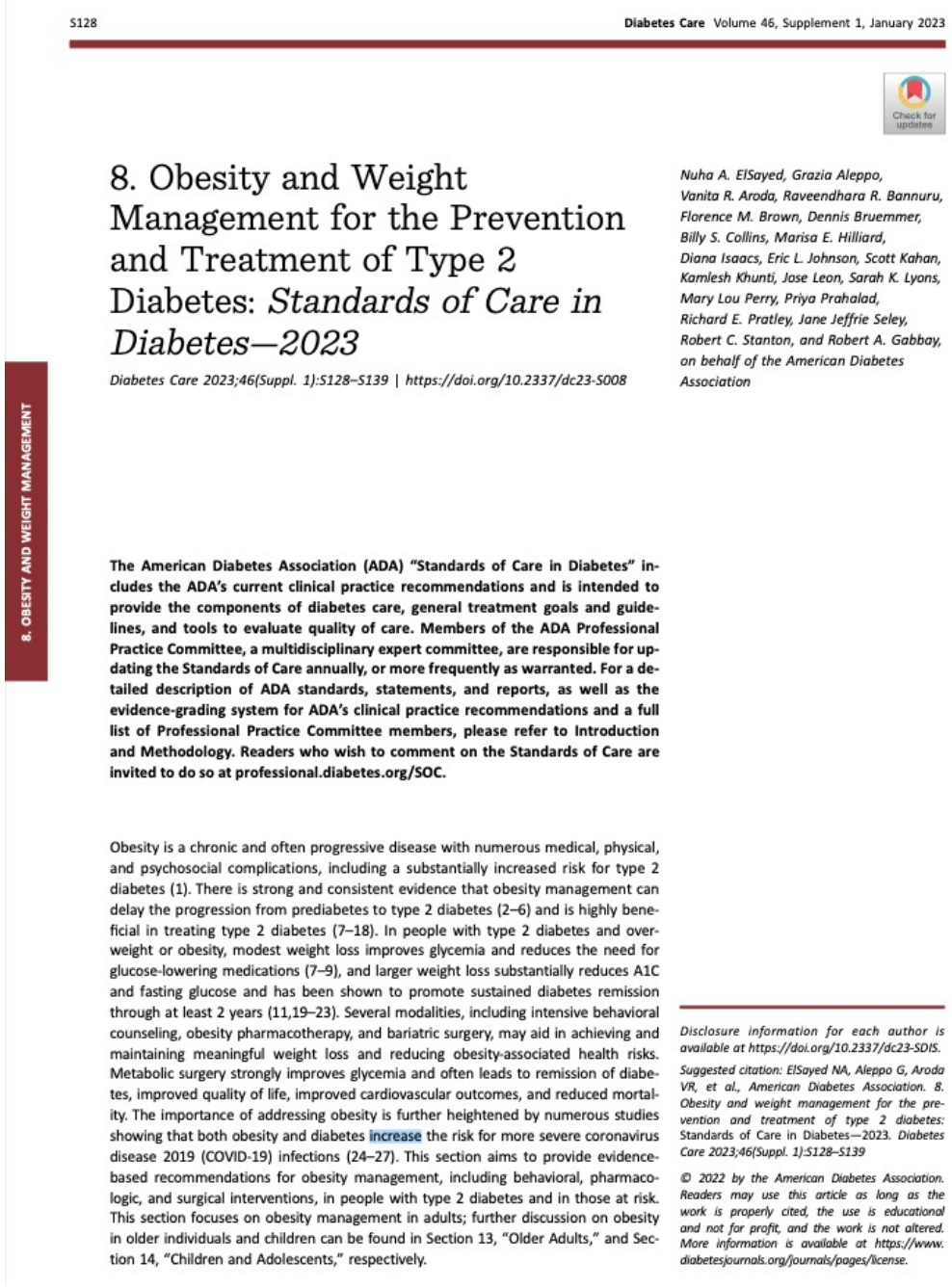


No. at risk

Nonsurgical controls	11435	8050	4791	2244	838
Metabolic surgery	2287	1372	910	535	293

MACE composite of 6 outcomes:
First occurrence of coronary artery events, cerebrovascular events, heart failure, atrial fibrillation, nephropathy, and all-cause mortality

JAMA. 2019;322(13):1271-1282



8. OBESITY AND WEIGHT MANAGEMENT

8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S128–S139 | https://doi.org/10.2337/dc23-S008

Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, and Robert A. Gabbay, on behalf of the American Diabetes Association

The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Obesity is a chronic and often progressive disease with numerous medical, physical, and psychosocial complications, including a substantially increased risk for type 2 diabetes (1). There is strong and consistent evidence that obesity management can delay the progression from prediabetes to type 2 diabetes (2–6) and is highly beneficial in treating type 2 diabetes (7–18). In people with type 2 diabetes and overweight or obesity, modest weight loss improves glycemia and reduces the need for glucose-lowering medications (7–9), and larger weight loss substantially reduces A1C and fasting glucose and has been shown to promote sustained diabetes remission through at least 2 years (11,19–23). Several modalities, including intensive behavioral counseling, obesity pharmacotherapy, and bariatric surgery, may aid in achieving and maintaining meaningful weight loss and reducing obesity-associated health risks. Metabolic surgery strongly improves glycemia and often leads to remission of diabetes, improved quality of life, improved cardiovascular outcomes, and reduced mortality. The importance of addressing obesity is further heightened by numerous studies showing that both obesity and diabetes increase the risk for more severe coronavirus disease 2019 (COVID-19) infections (24–27). This section aims to provide evidence-based recommendations for obesity management, including behavioral, pharmacologic, and surgical interventions, in people with type 2 diabetes and in those at risk. This section focuses on obesity management in adults; further discussion on obesity in older individuals and children can be found in Section 13, "Older Adults," and Section 14, "Children and Adolescents," respectively.

Disclosure information for each author is available at https://doi.org/10.2337/dc23-SDIS.

Suggested citation: ElSayed NA, Aleppo G, Aroda VR, et al., American Diabetes Association. 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: Standards of Care in Diabetes—2023. Diabetes Care 2023;46(Suppl. 1):S128–S139

ADA Standards of Care 2023

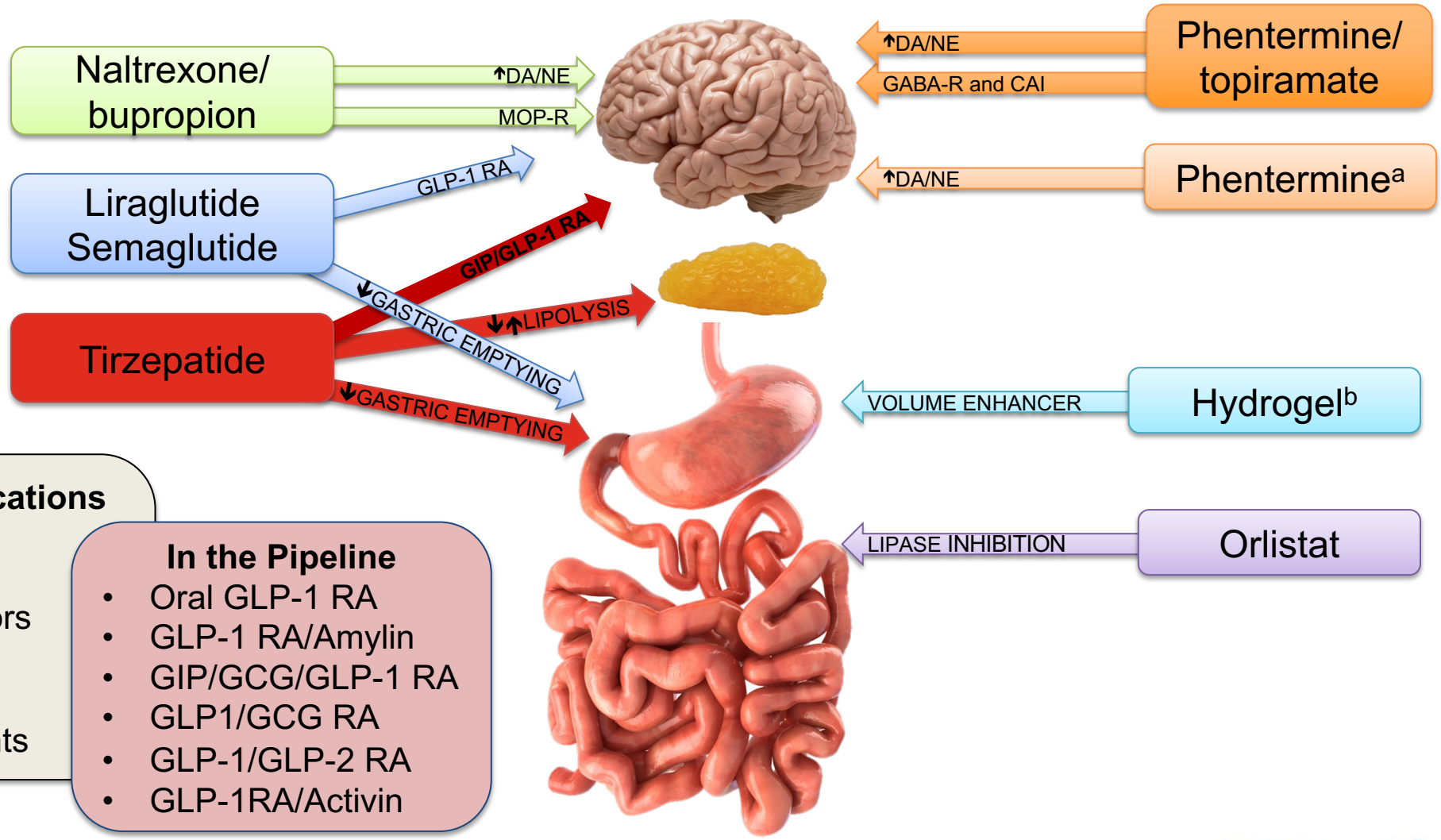
Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes

Metabolic surgery **should be a recommended option to treat type 2 diabetes in adults with BMI 35.0– 39.9 kg/m2 (32.5–37.4 kg/m2 in Asian American individuals**) who do not achieve durable weight loss with nonsurgical methods

Metabolic surgery **may be considered as an option to treat type 2 diabetes in adults with BMI 30.0–34.9 kg/m2 (27.5–32.4 kg/m2 in Asian American individuals)** who do not achieve durable weight loss with nonsurgical methods

FDA-Approved Anti-Obesity Medications

BMI ≥30 or ≥27 kg/m2 + ≥1 complication



Off-Label Medications

- Metformin
- GLP-1 RAs
- SGLT2 inhibitors
- Topiramate
- Bupropion
- Other stimulants

In the Pipeline

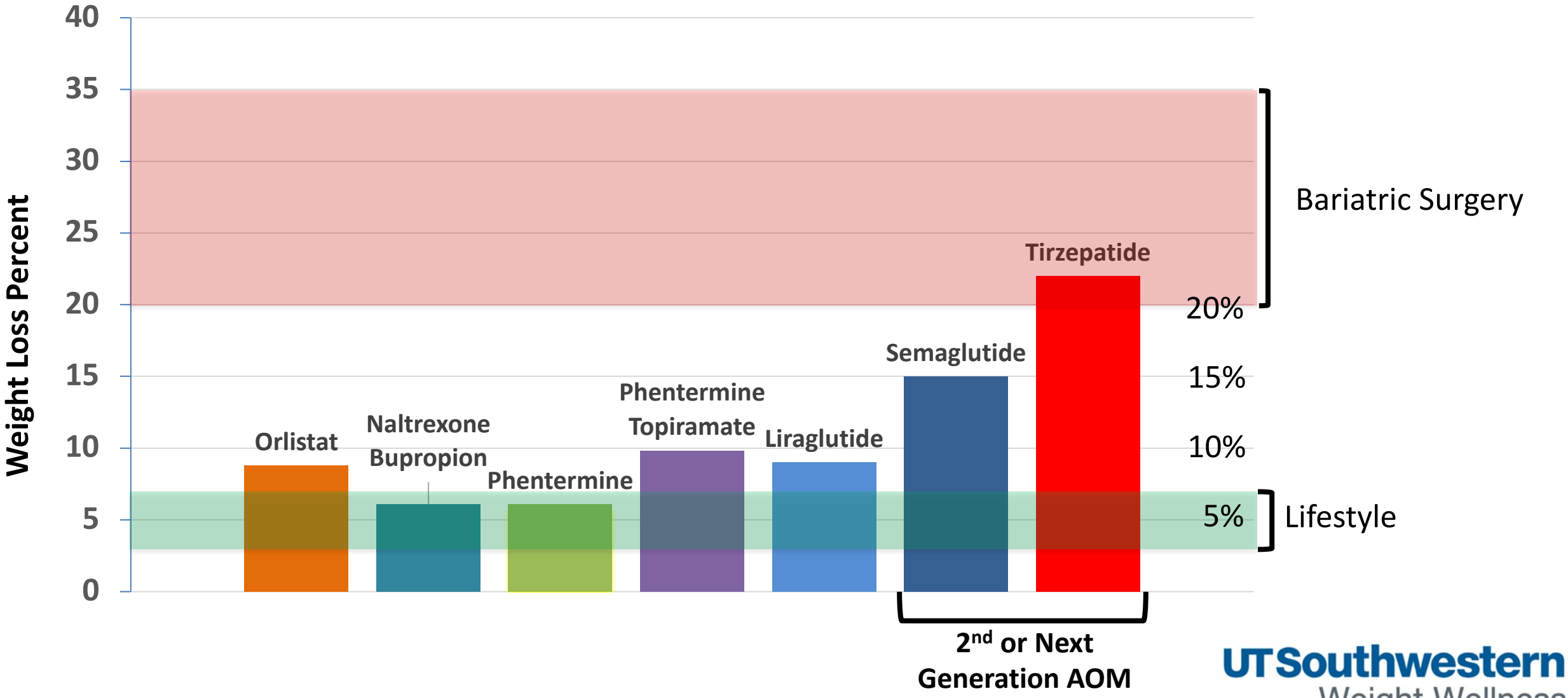
- Oral GLP-1 RA
- GLP-1 RA/Amylin
- GIP/GCG/GLP-1 RA
- GLP1/GCG RA
- GLP-1/GLP-2 RA
- GLP-1RA/Activin

[a] Approved for short-term use only. [b] Considered a medical device not a medication, because it does not act systemically.

1. Tak YJ, Lee SY. *Curr Obes Rep*. 2021;10:14-30. 2. Giruzzi N. *Clin Diabetes*. 2020;38:313-314. 3. Angelidi AM et al. *Endocr Rev*. 2022;43:507-557.
4. Brandt SJ et al. *Peptides*. 2018;100:190-201. 5. Tschöp M et al. *Diabetologia*. 2023 May 20. Online ahead of print.

UT Southwestern Weight Wellness

Effectiveness of Anti-Obesity Medications vs. Lifestyle and Bariatric Surgery for Treating Obesity



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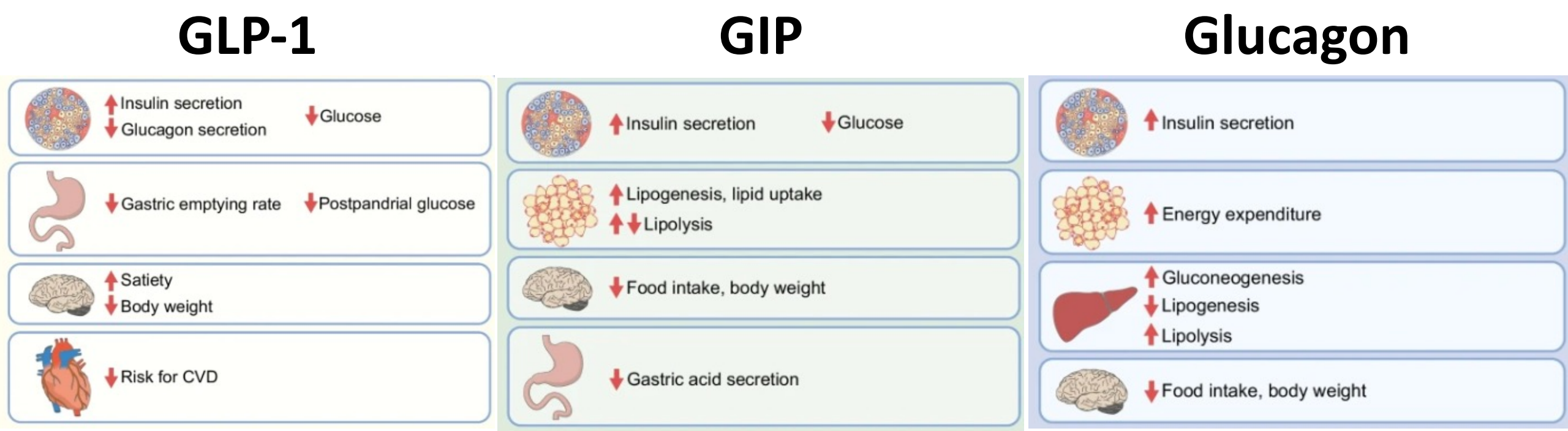
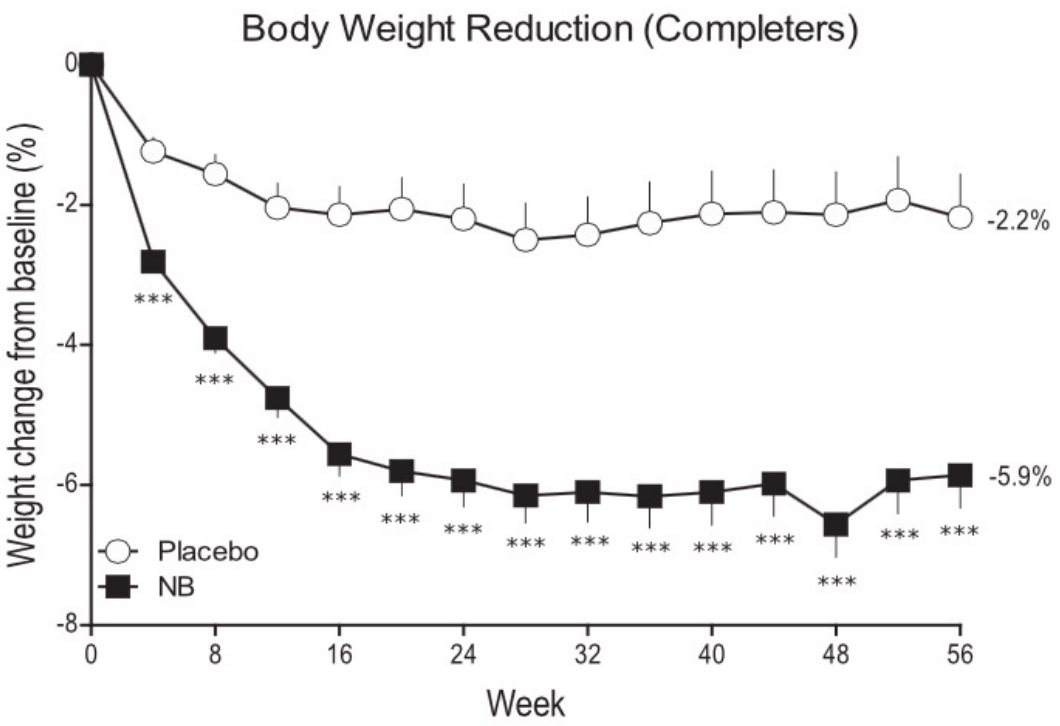
Multi-Receptor Agonism for T2D and Obesity

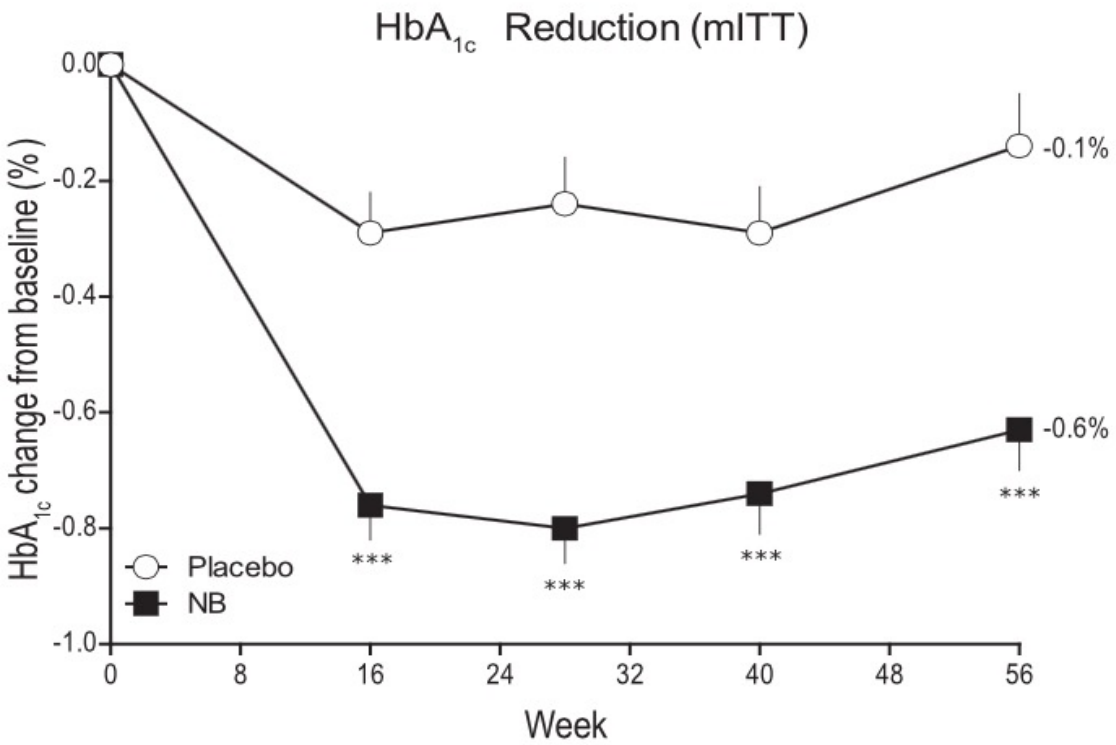


Tschöp et al. Diabetologia May 20, 2023

Naltrexone/Bupropion in People with T2DM



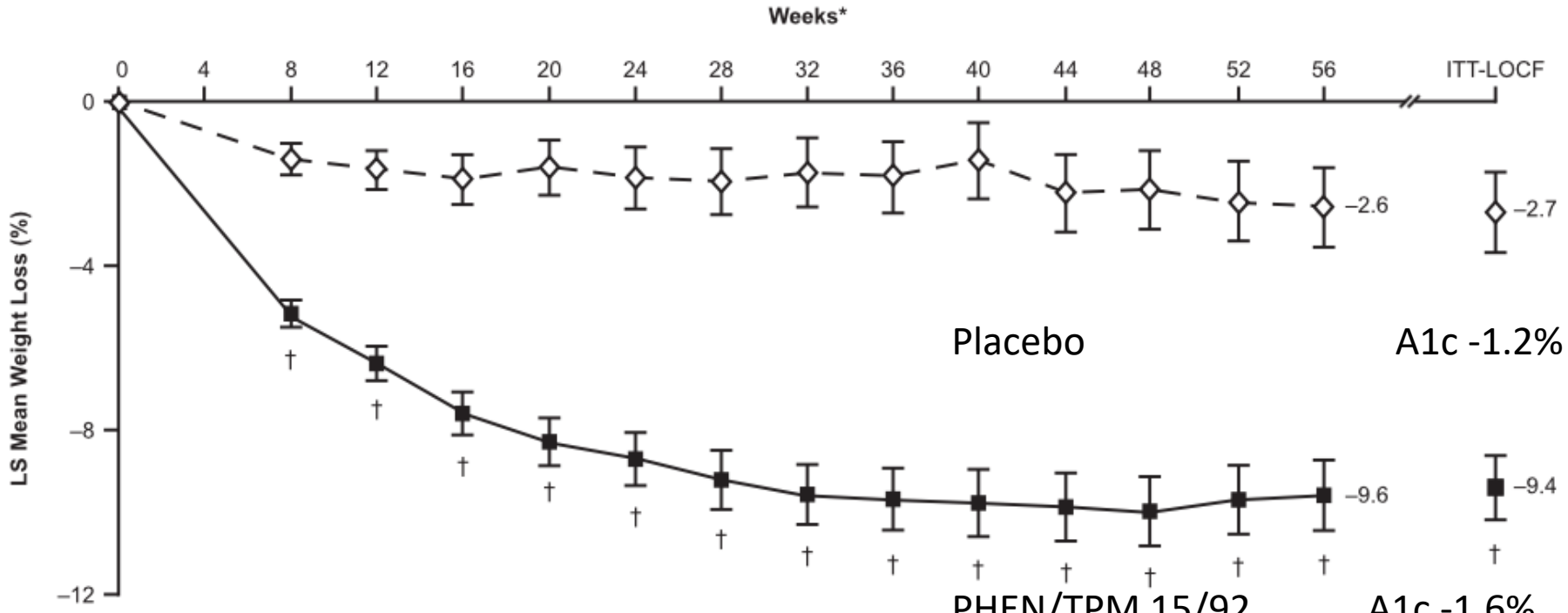
Weight Loss at Week 56	Placebo (% subjects)	NB (% subjects)
≥ 5%	24.0	53.1***
≥ 10%	8.0	26.3***



HbA_{1c} Target at Week 56	Placebo (% subjects)	NB (% subjects)
< 7%	26.3	44.1***
< 6.5%	10.2	20.7**

Diabetes Care 2013; 36:4022–4029

Phentermine Topiramate ER in T2DM

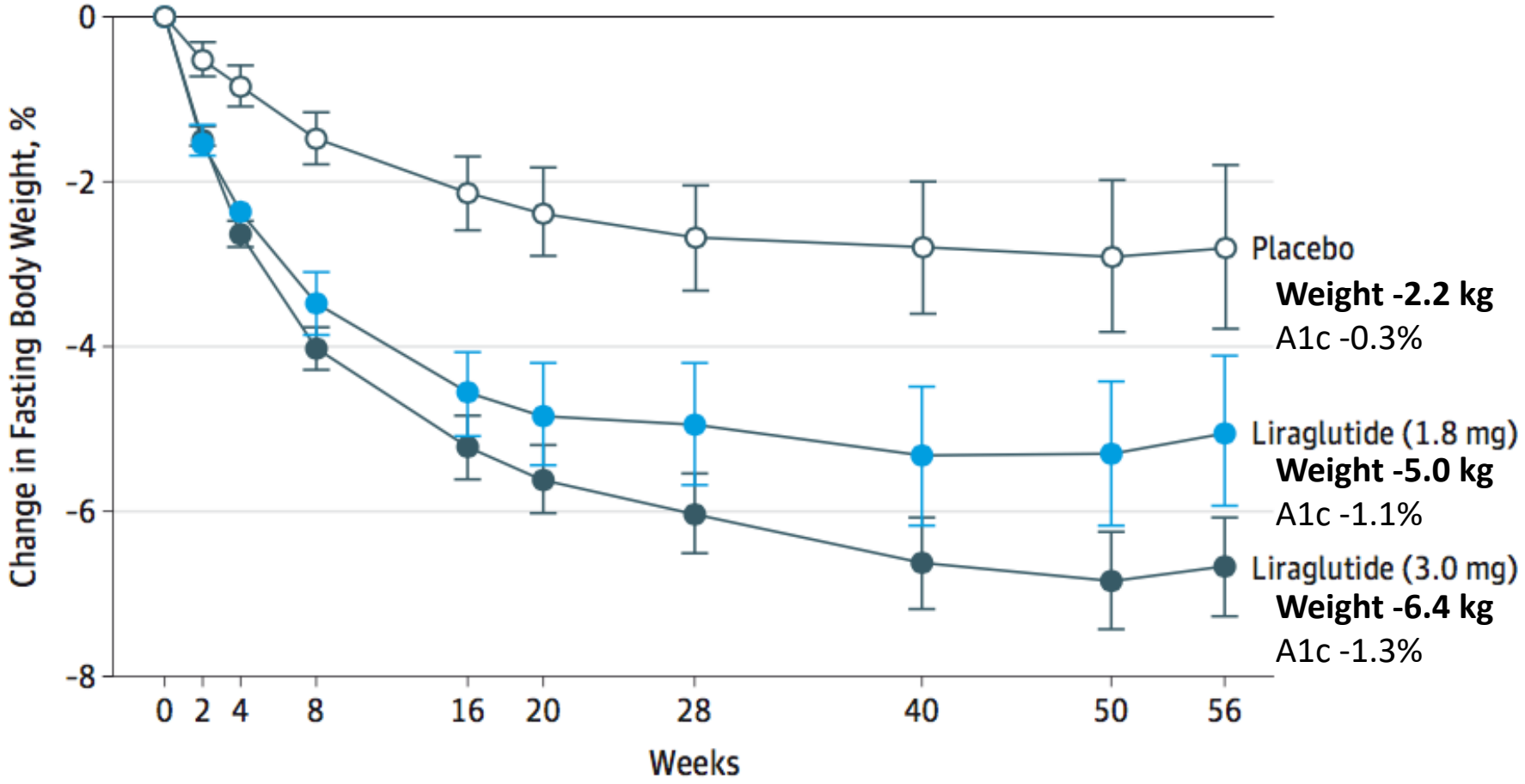


mITT, n													ITT-LOCF
Placebo	52	51	52	52	52	52	52	52	52	52	51	52	55
PHEN/TPM ER 15/92	68	68	68	68	68	68	68	68	68	68	66	68	75

Diabetes Care 2014;37:3309–3316

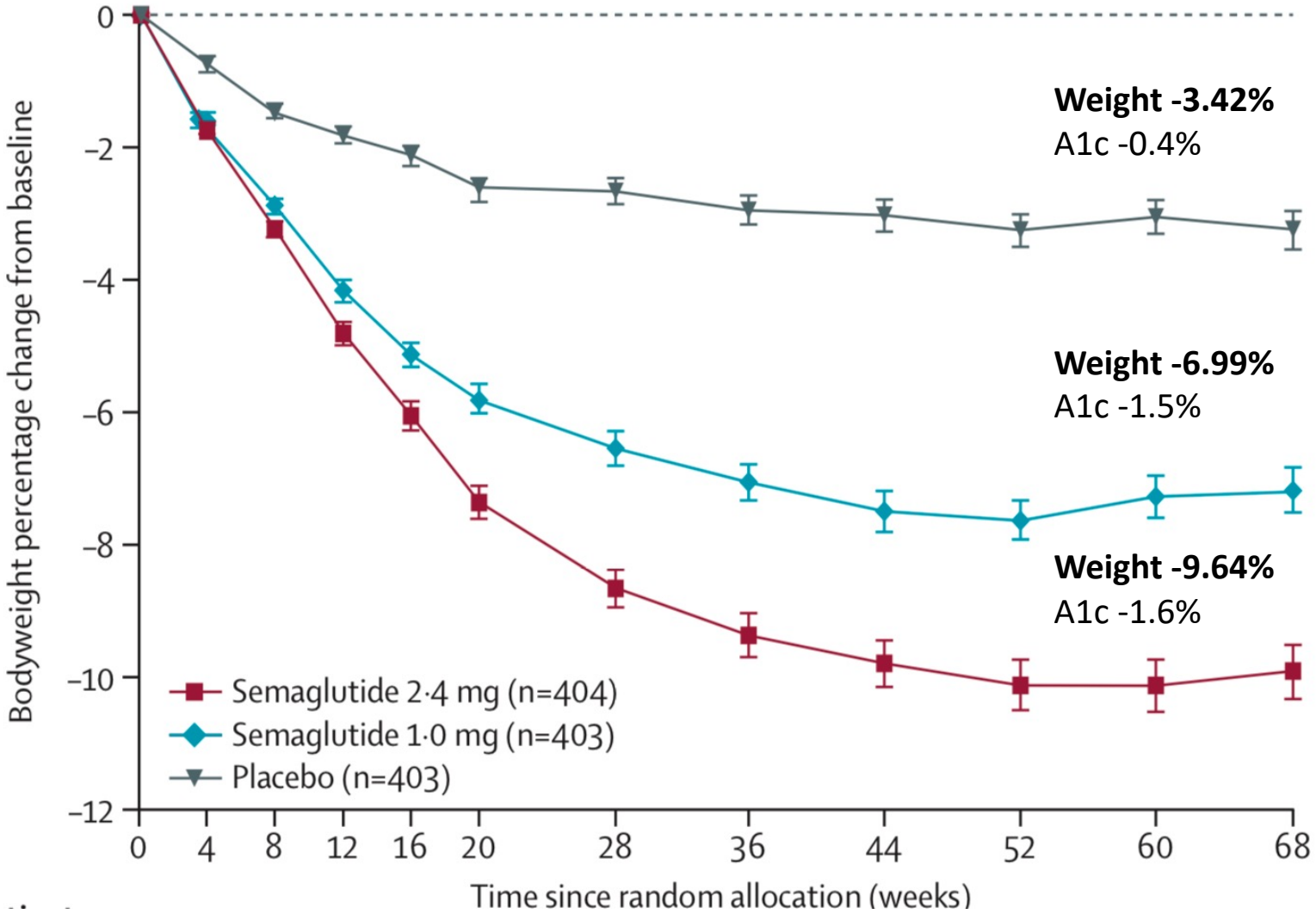
Liraglutide 1.8 and 3 mg in People with T2DM

SCALE Diabetes



JAMA 2015;314(7);687-699

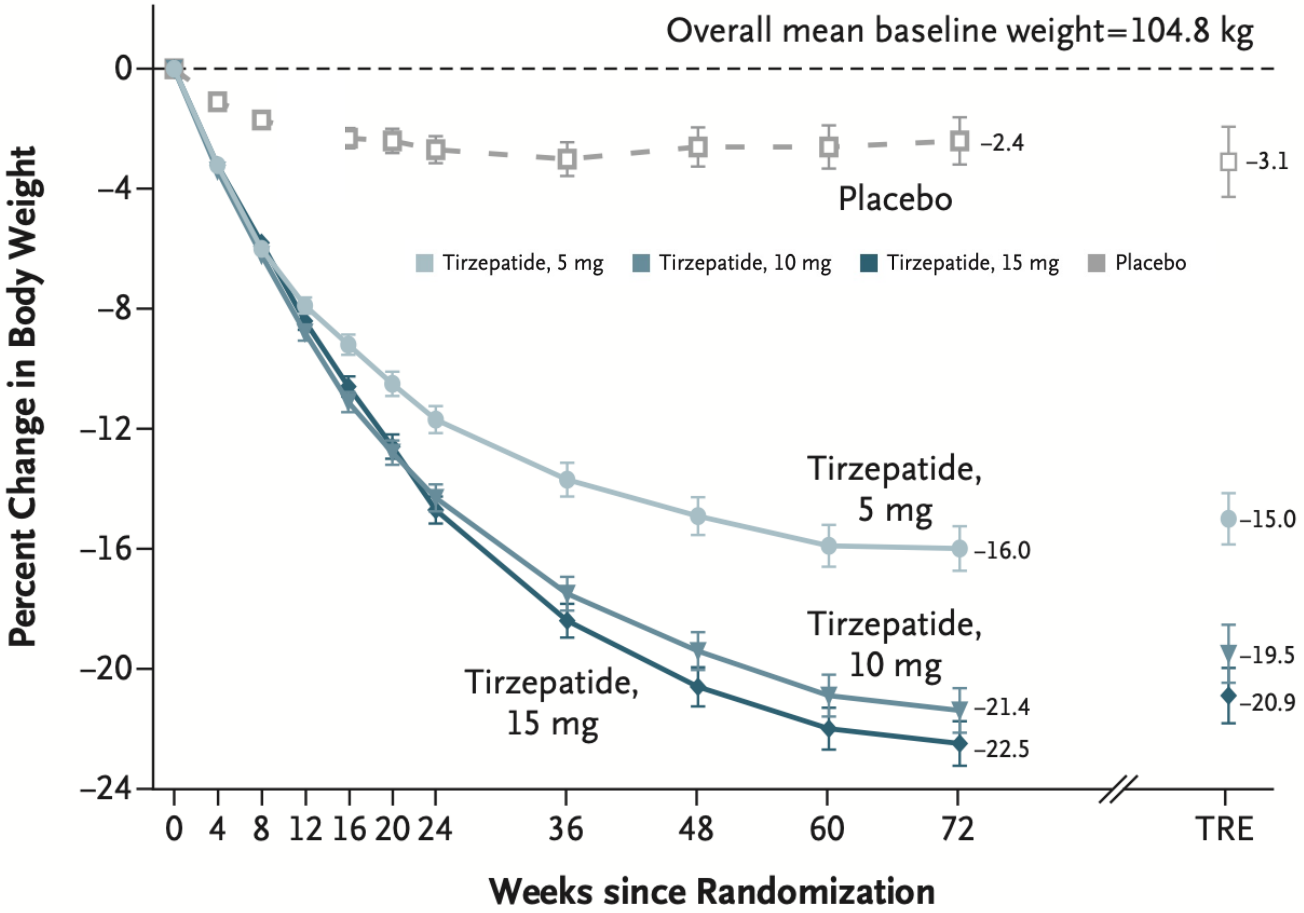
Semaglutide 2.4 mg in People with T2DM
STEP-2



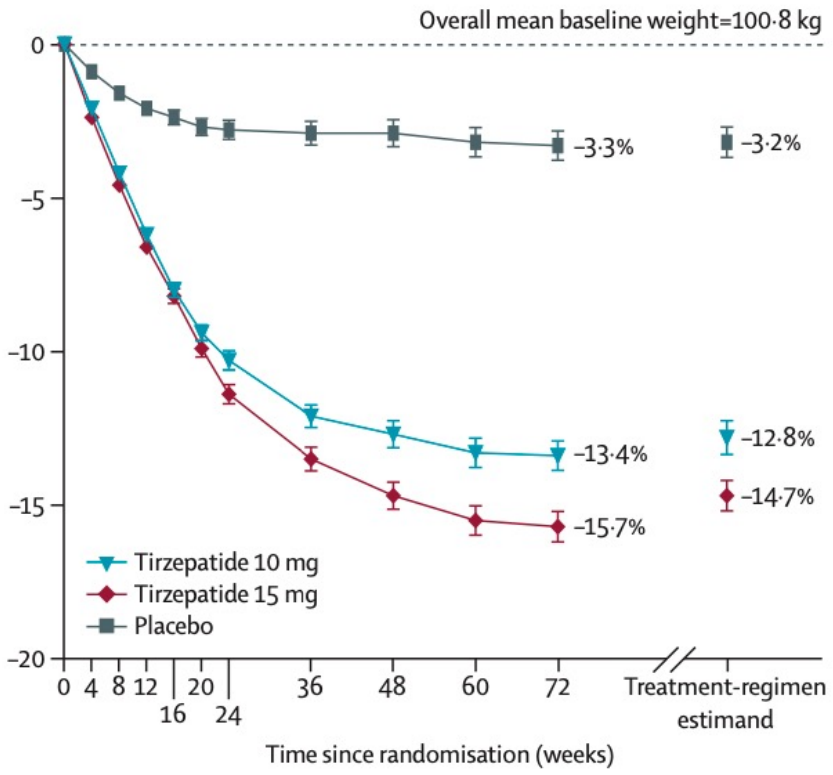
Davies et al. Lancet 2021; 397: 971–84

TZP for Treating Obesity in PwO ±T2D

SURMOUNT-1 PwO without T2D

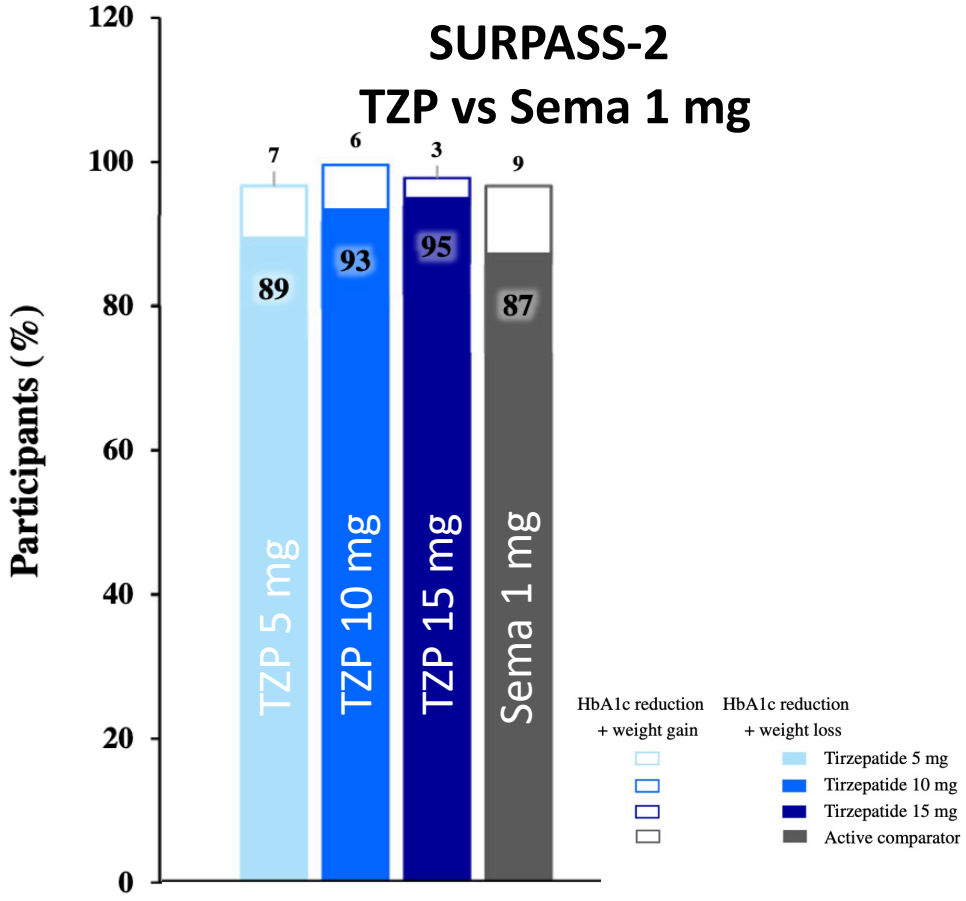


SURMOUNT-2 PwO with T2D

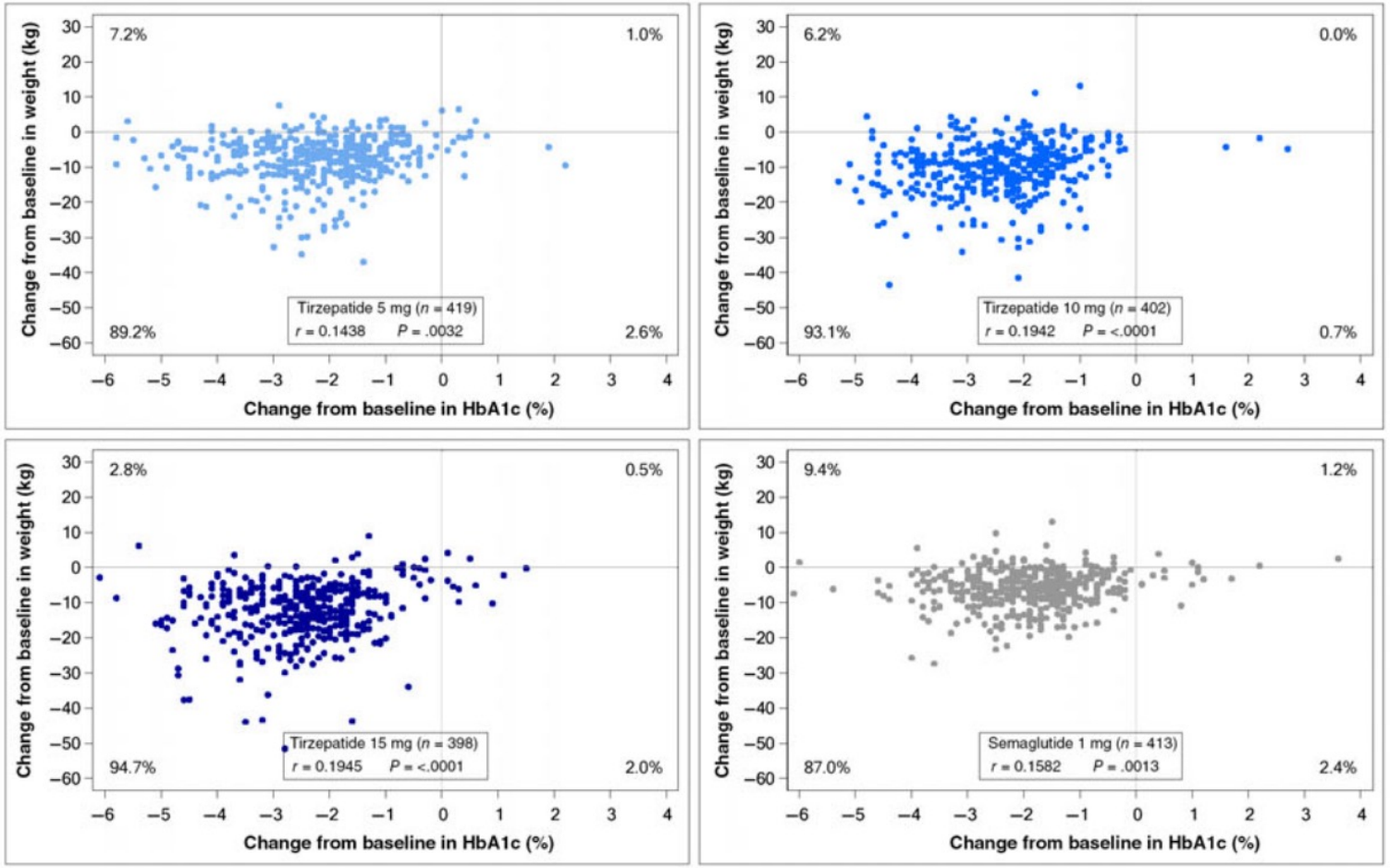


Jastreboff et al. N Engl J Med 2022;387:205-16
Garvey et al. Lancet 2023; 402: 613–26

Reduction in Weight Correlates with A1c Reduction with TZP in SURPASS-2, 3, 4



Participants with HbA1c reduction + weight loss (solid bars) and HbA1c reduction or no weight change or weight gain (open bars)



Pedersen S et al. Diabetes Obes Metab.2023;25:2553–2560

Practical Pearls for Incretin Side Effects

Review the MOA and Anticipate Side Effects

- Eat slowly and stop when hunger disappears
- Don’t feed the nausea
- Adjust the dose
- Consider anti-nausea medications

Constipation or Diarrhea

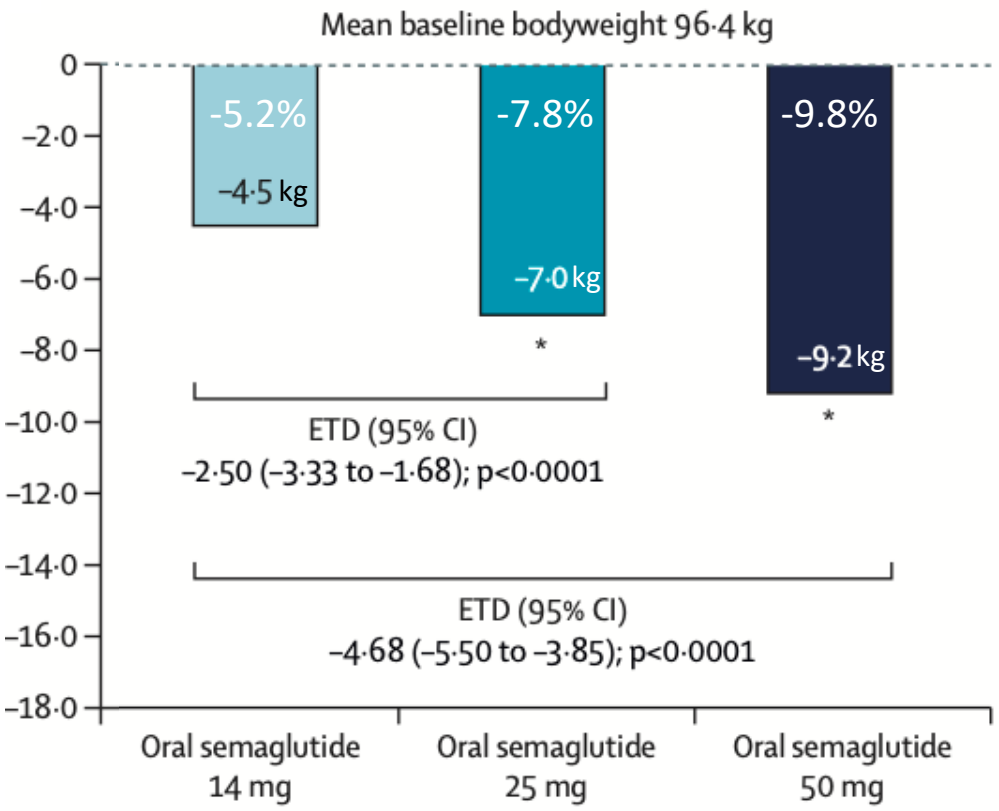
- Be proactive with psyllium fiber
- Consider stool softeners for constipation
- Consider bile acid sequestrant for diarrhea

Abdominal Pain on a GLP-1 RA

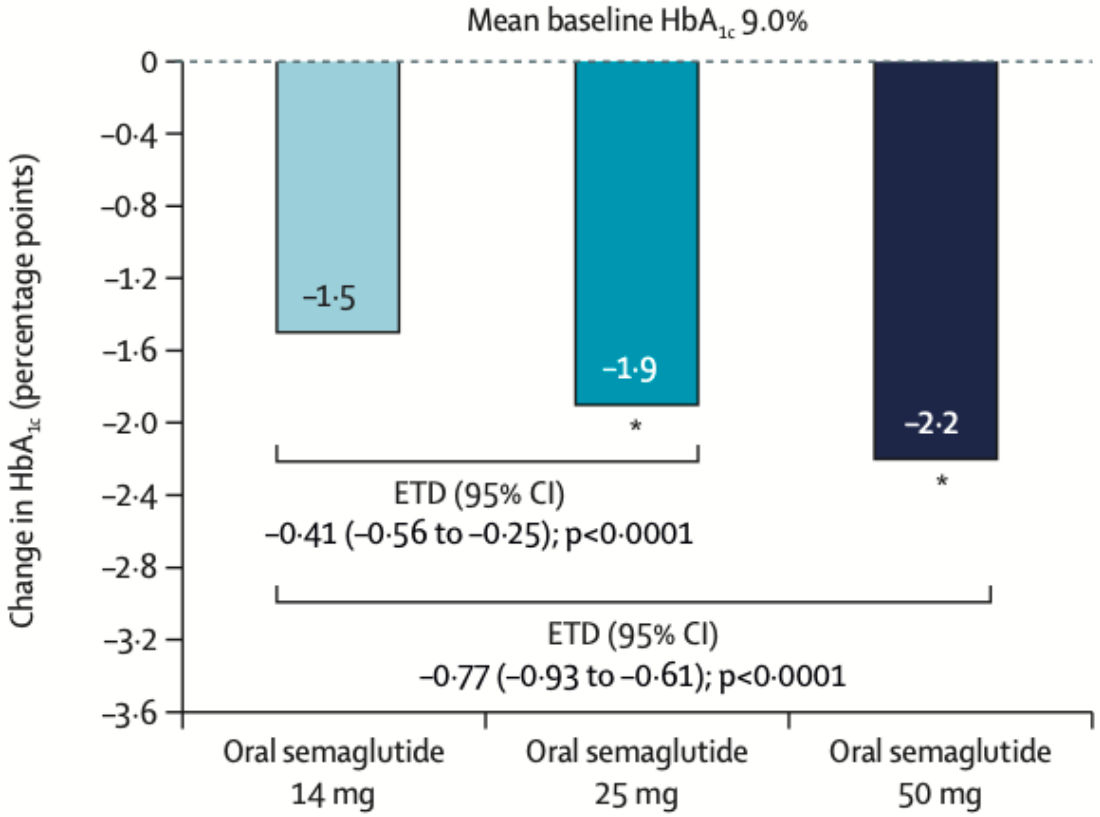
- Is this bloating or pancreatitis?
- Check a lipase, CMP, CBC, UA
- If lipase elevated, stop GLP-1 RA
- If gallbladder present, get RUQ US

Oral Semaglutide 25mg, 50 mg in PwT2D – PIONEER PLUS

Change in Body Weight

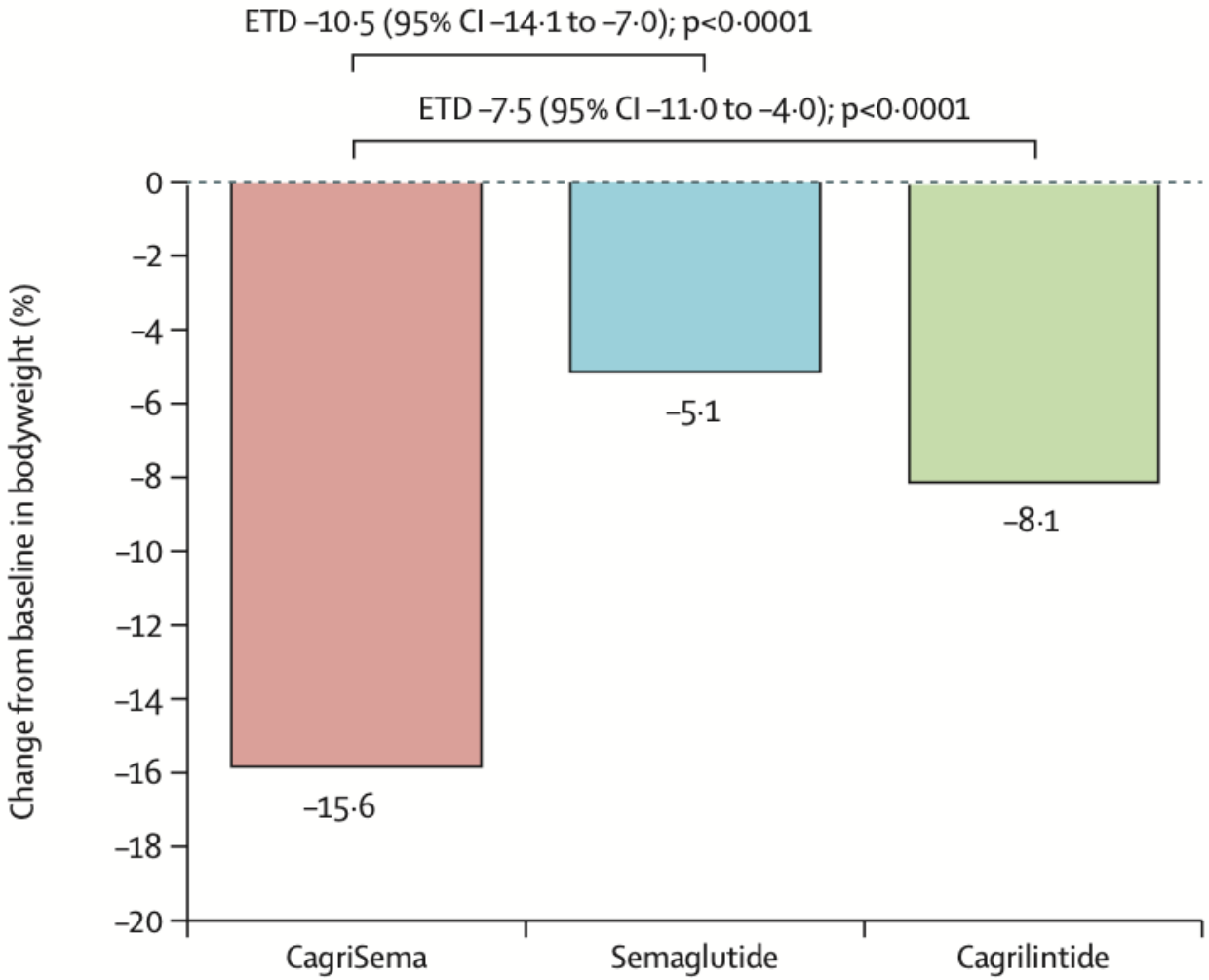


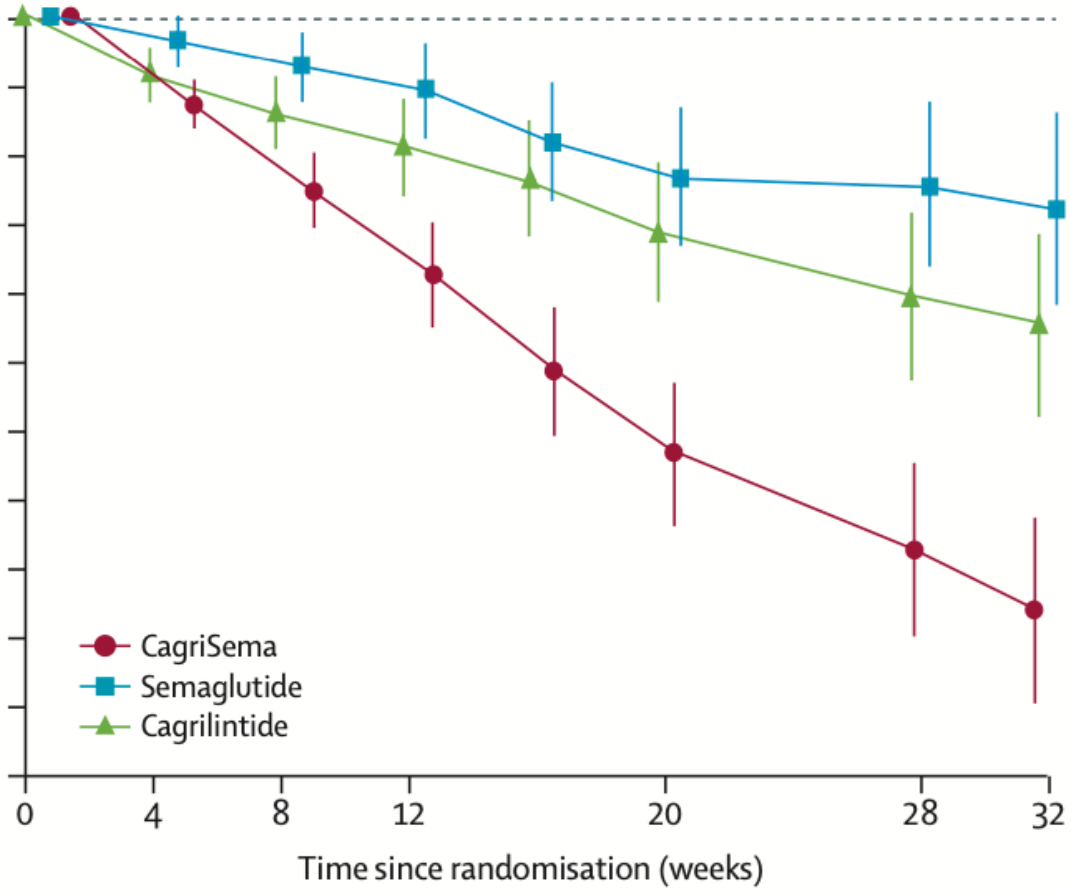
Change in HbA1c



Aroda et al. Lancet 2023; 402: 693–704

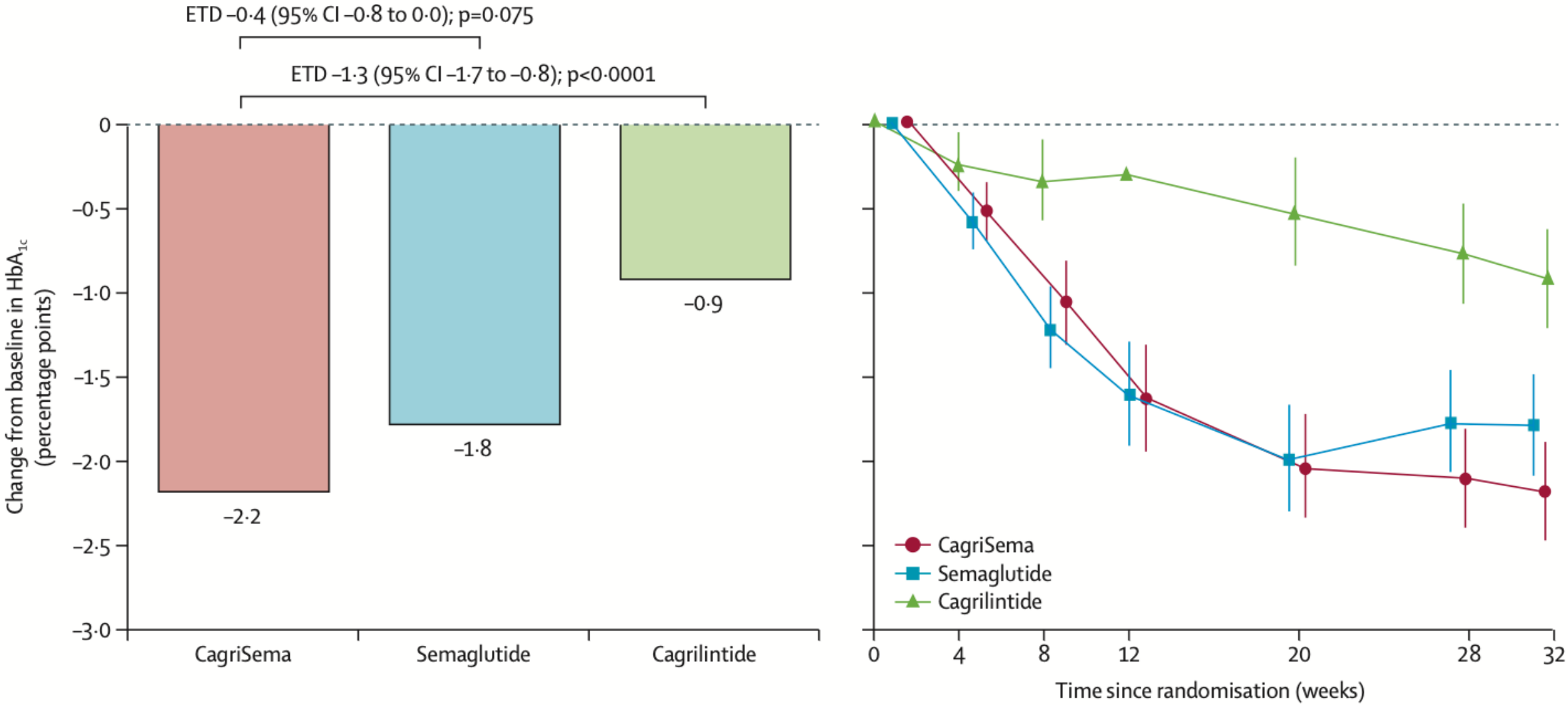
CagriSema vs. Sema vs. Cagrilintide on Weight in T2D





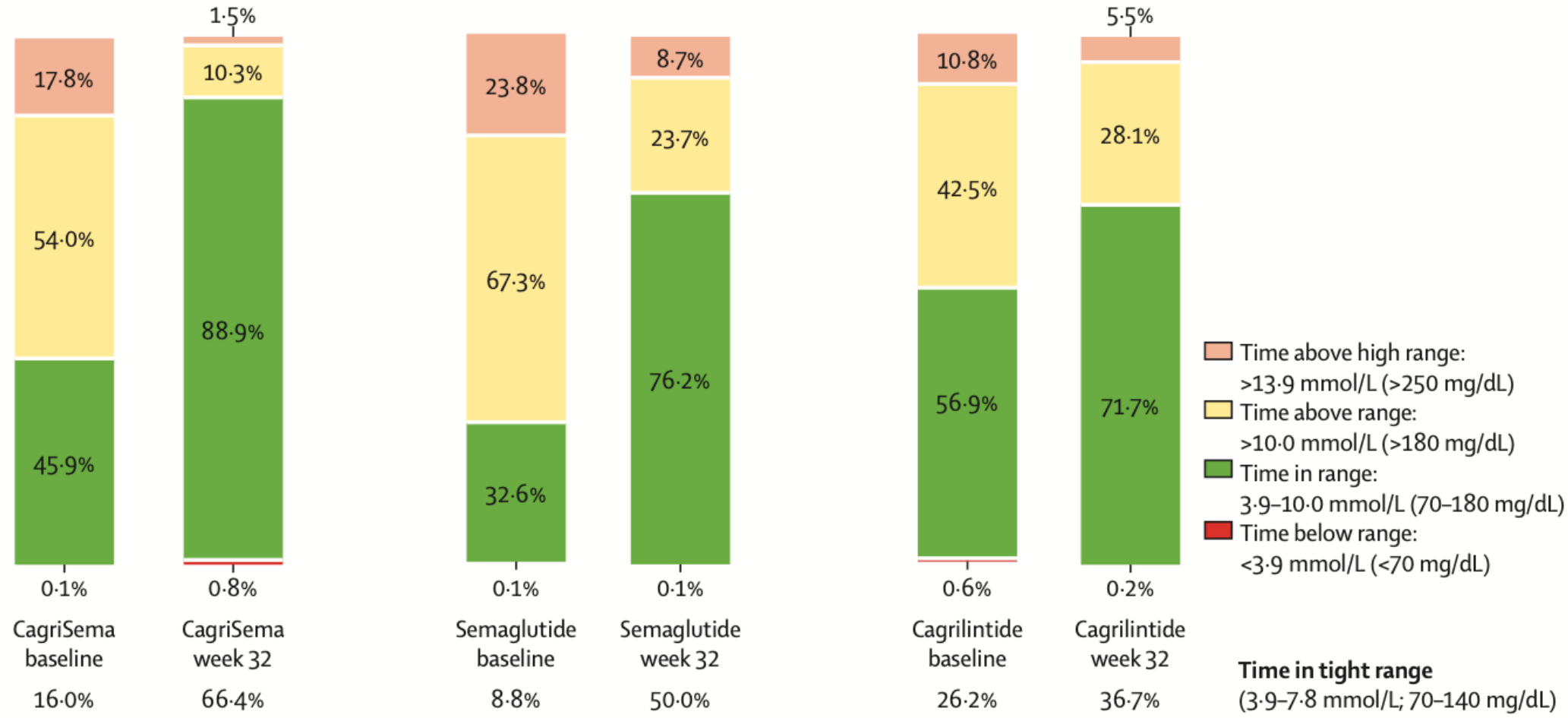
Frias JP et al. Lancet 2023; 402: 720-30

CagriSema vs. Sema vs. Cagrilintide on A1c in T2D



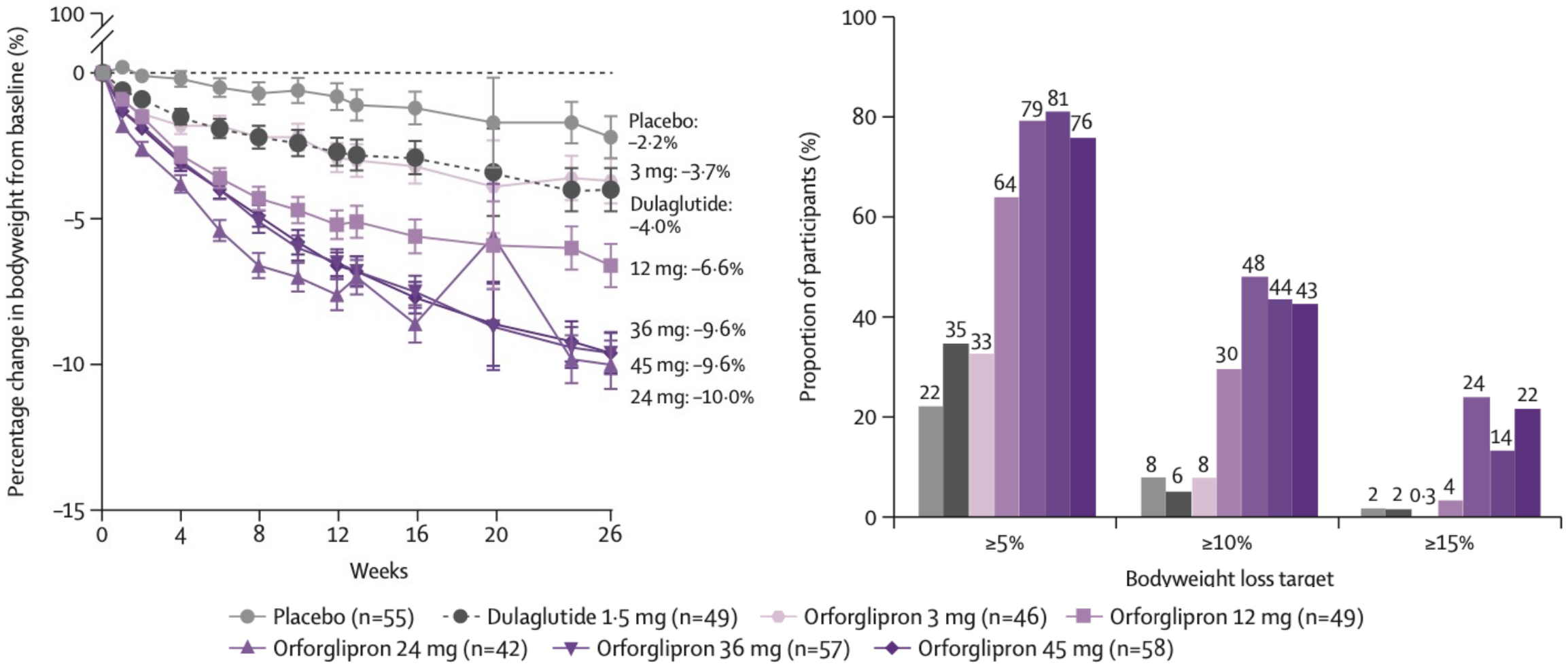
Frias JP et al. Lancet 2023; 402: 720-30

CagriSema vs. Sema vs. Cagrilintide on TIR in T2D



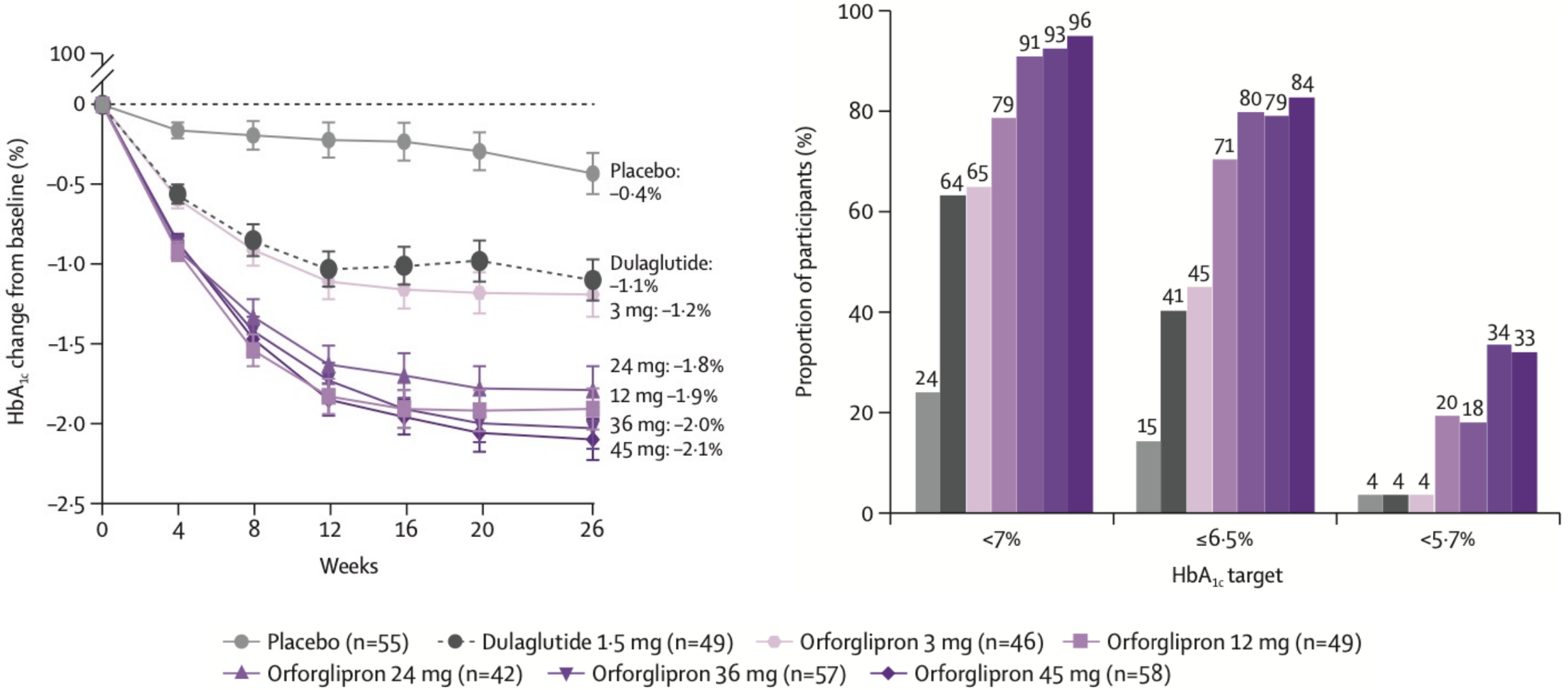
Frias JP et al. Lancet 2023; 402: 720-30

Orforglipron and Body Weight Changes in T2D



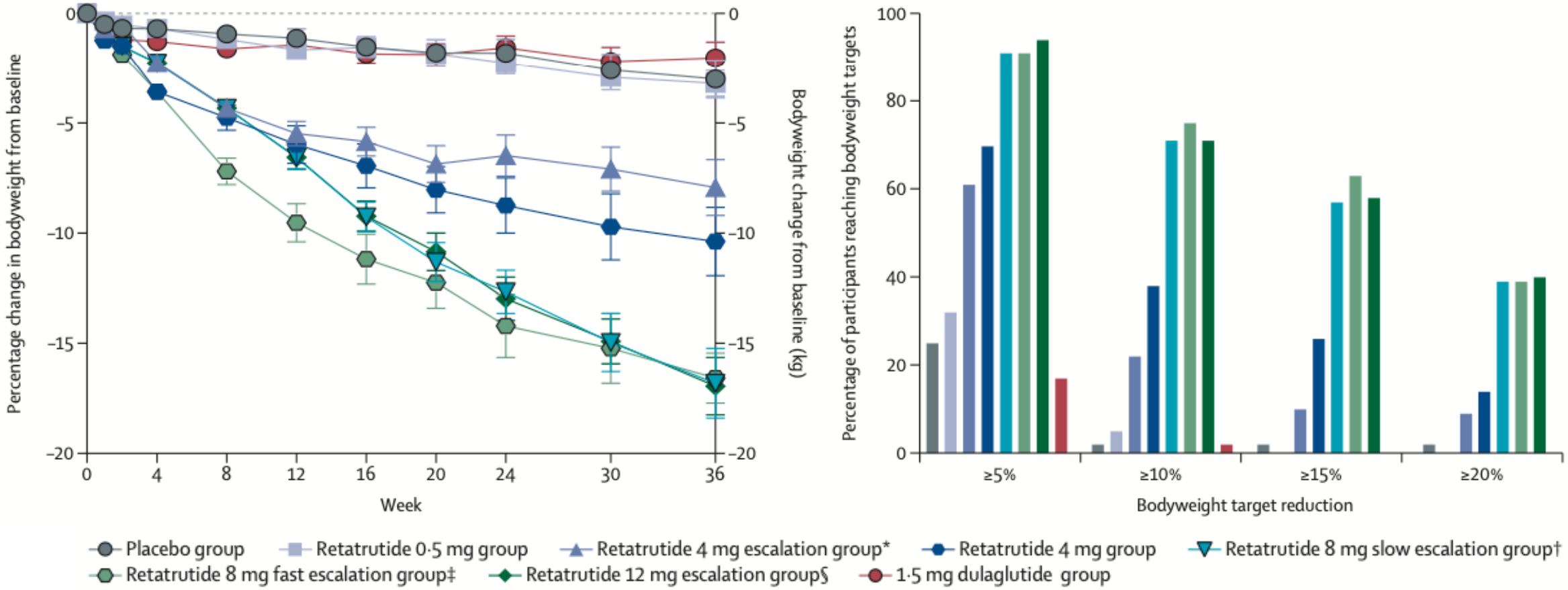
Frias JP et al. Lancet 2023; 402: 472–83

Orforglipron and A1c Changes in T2D



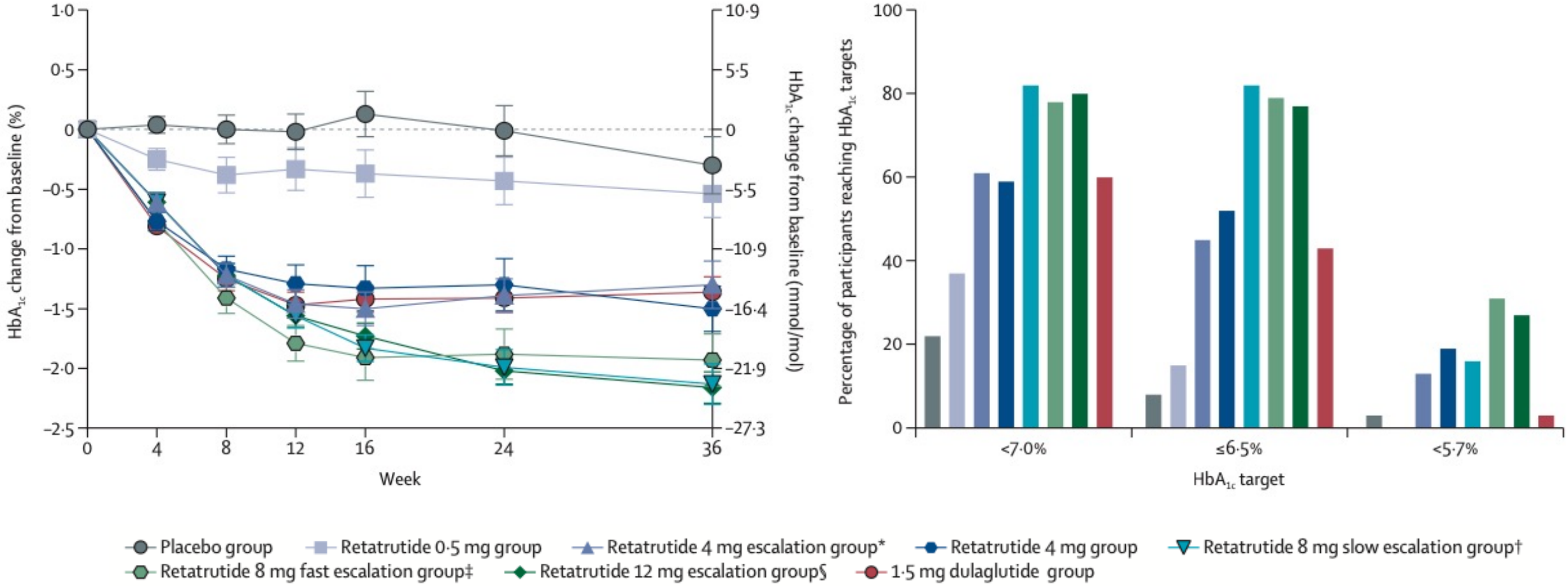
Frias JP et al. Lancet 2023; 402: 472–83

Retatrutide and Body Weight Changes in T2D



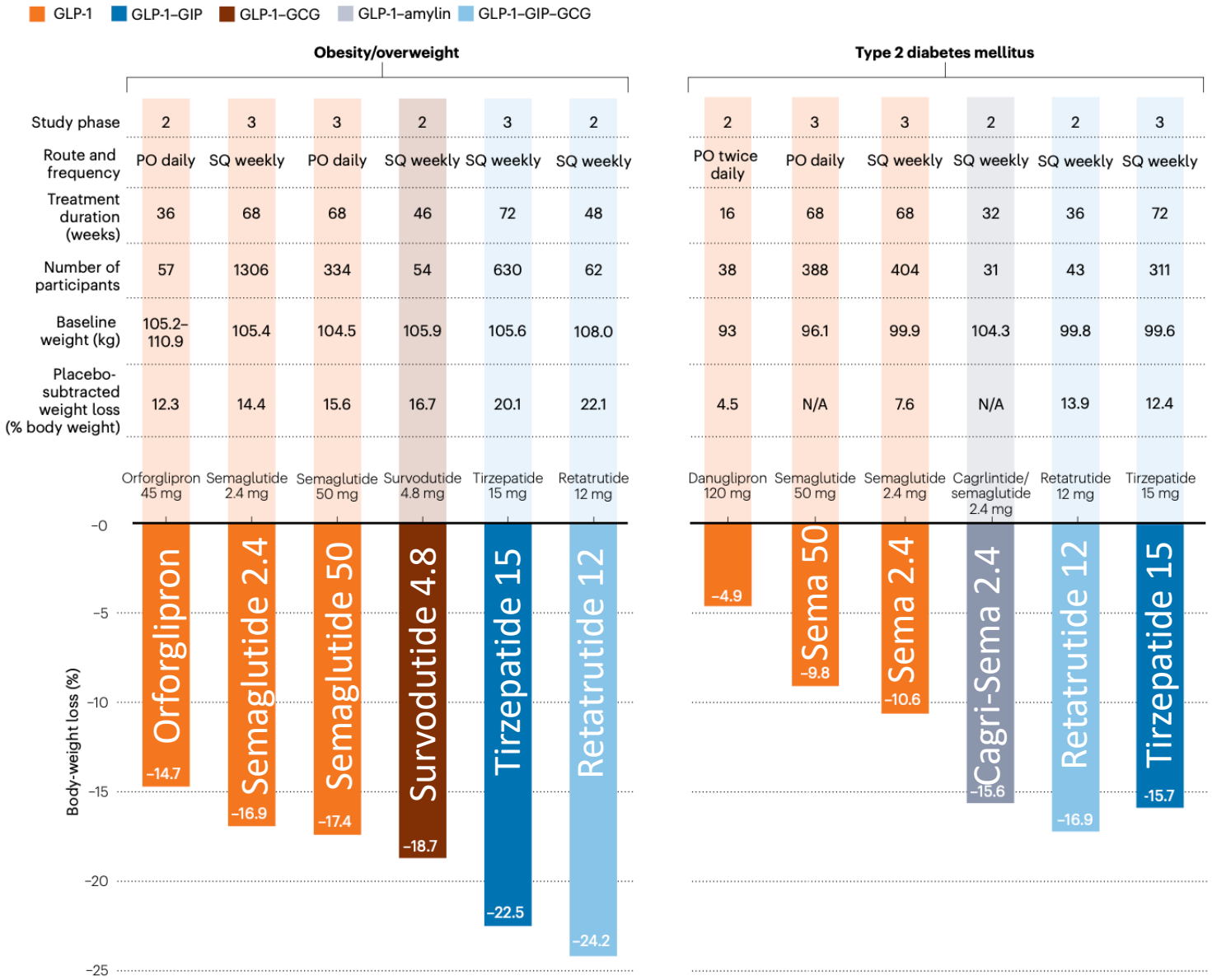
Rosenstock Lancet 2023; 402: 529–44

Retatrutide and A1c Changes in T2D



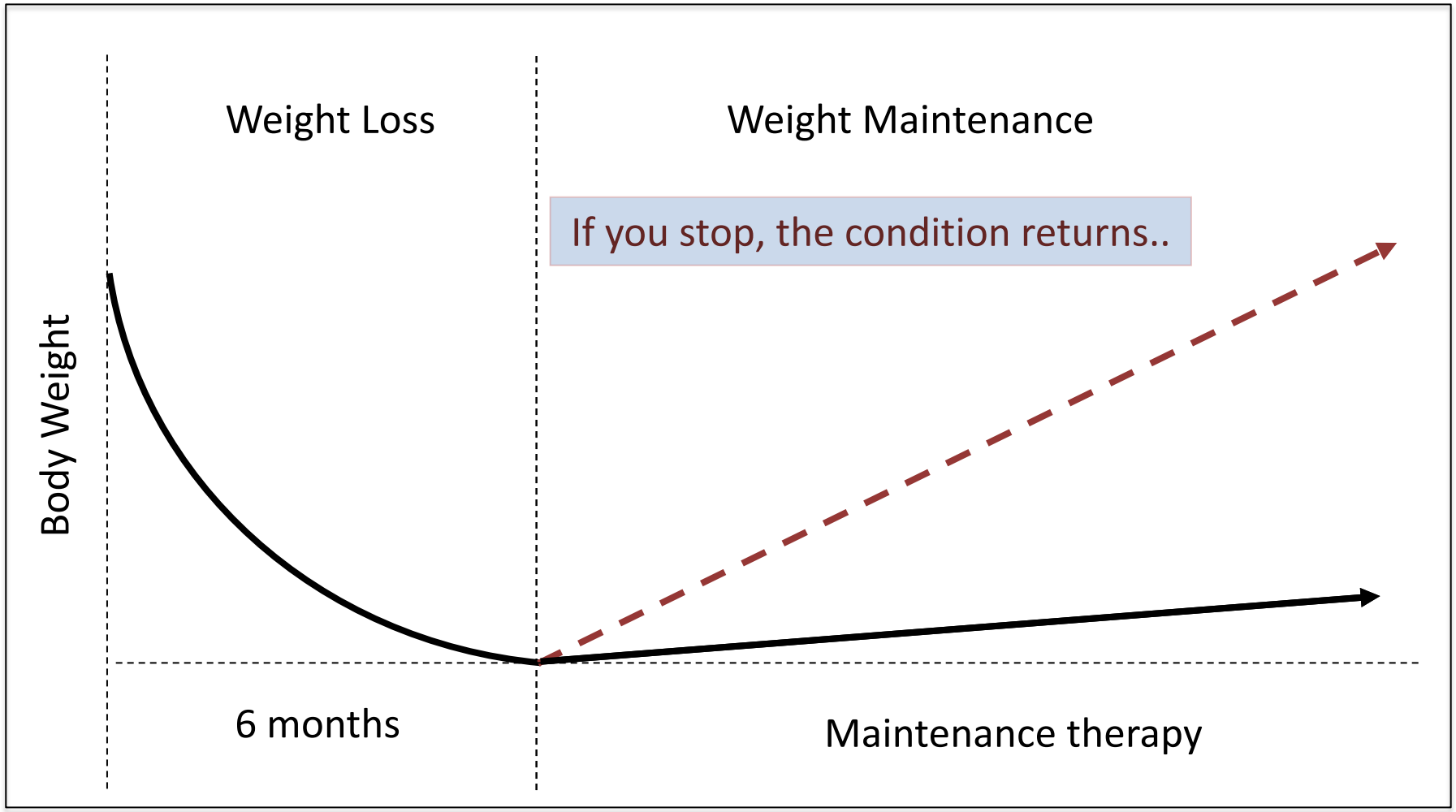
Rosenstock Lancet 2023; 402: 529–44

Emerging Next-Generation AOM



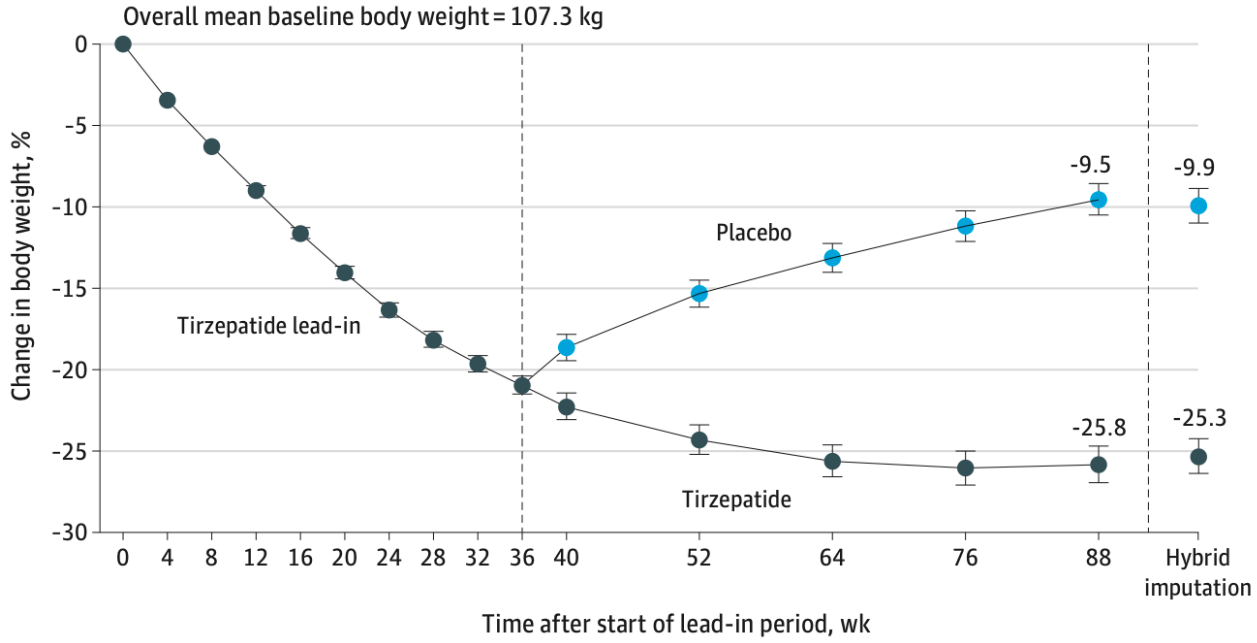
Lingvay, I., Agarwal, S. A revolution in obesity treatment. *Nat Med* (2023)

Think of Treating Obesity like Hypertension

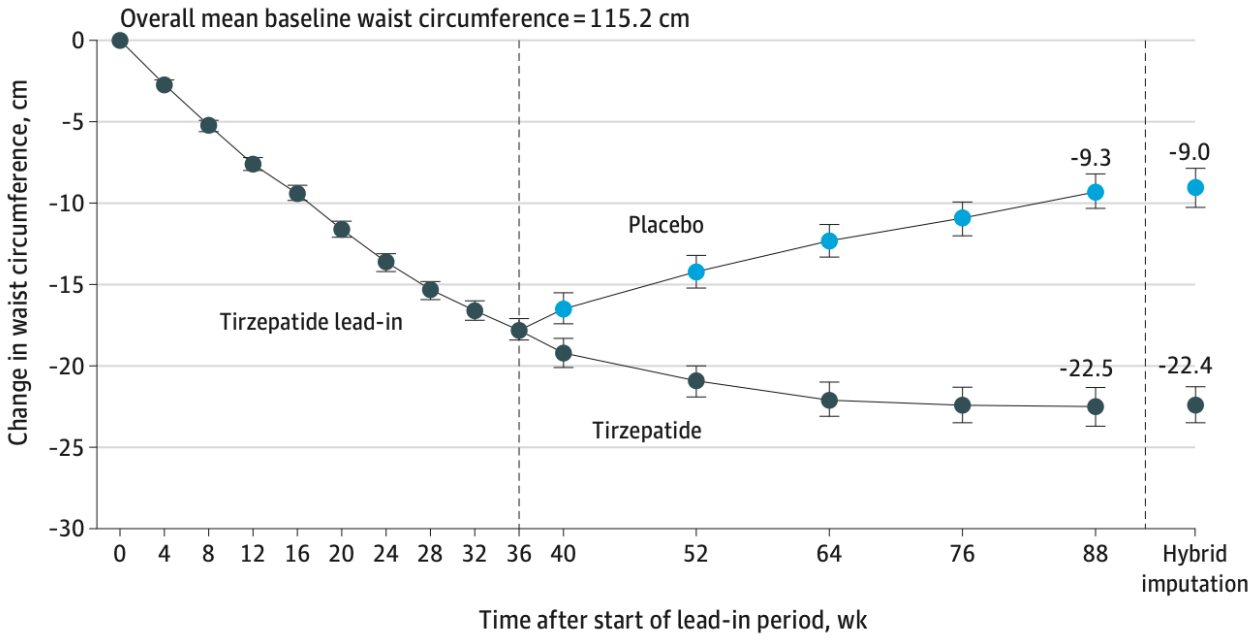


SURMOUNT 4 – Tirzepatide for Obesity

Changes in Body Weight



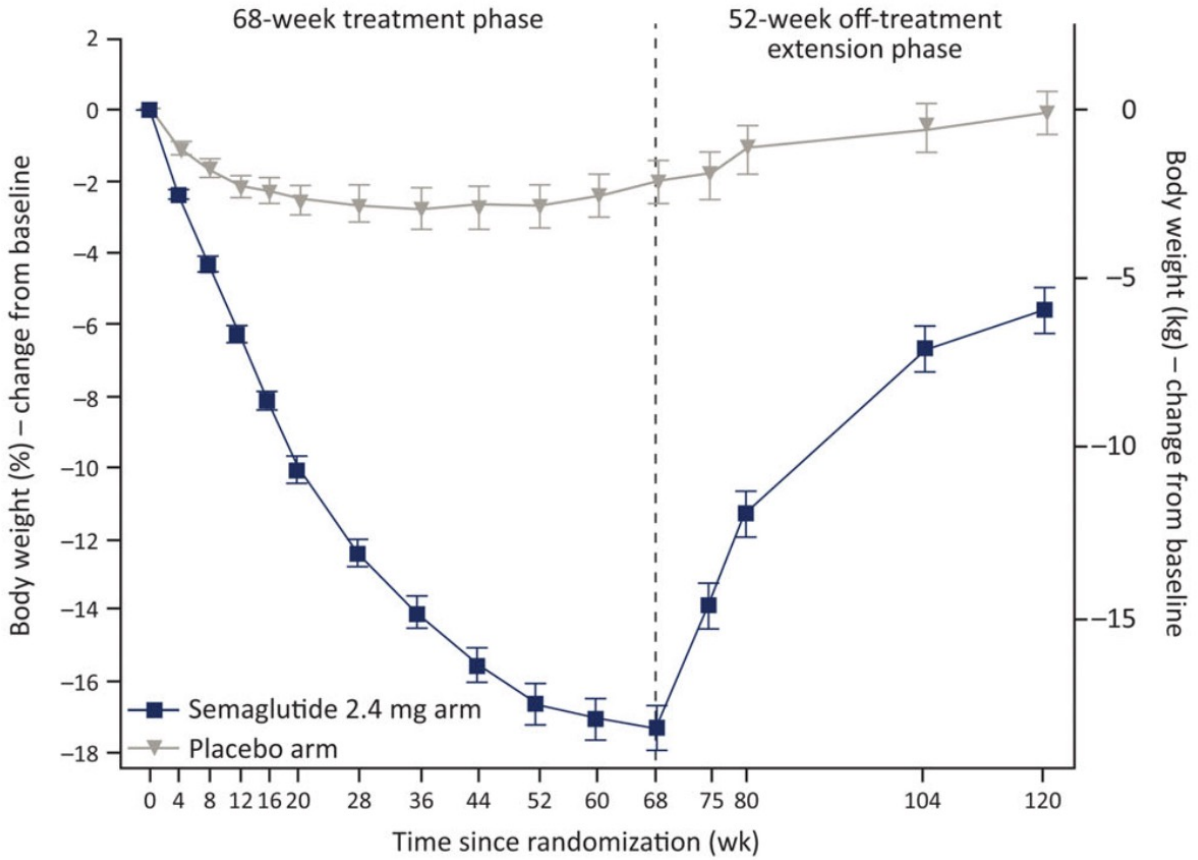
Change in Waist Circumference



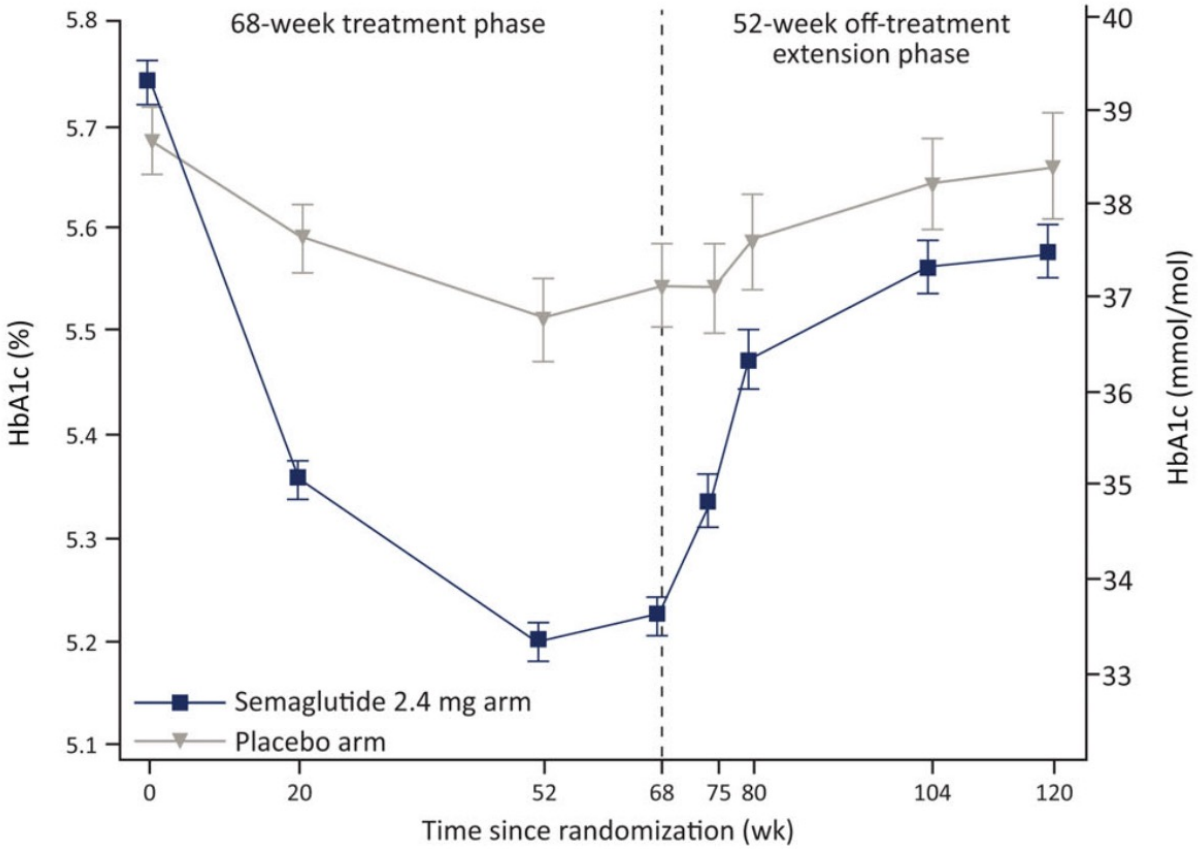
Aronne et al. *JAMA*. 2024;331(1):38-48

STEP 1 Study Extension - Semaglutide 2.4 mg

Changes in Body Weight

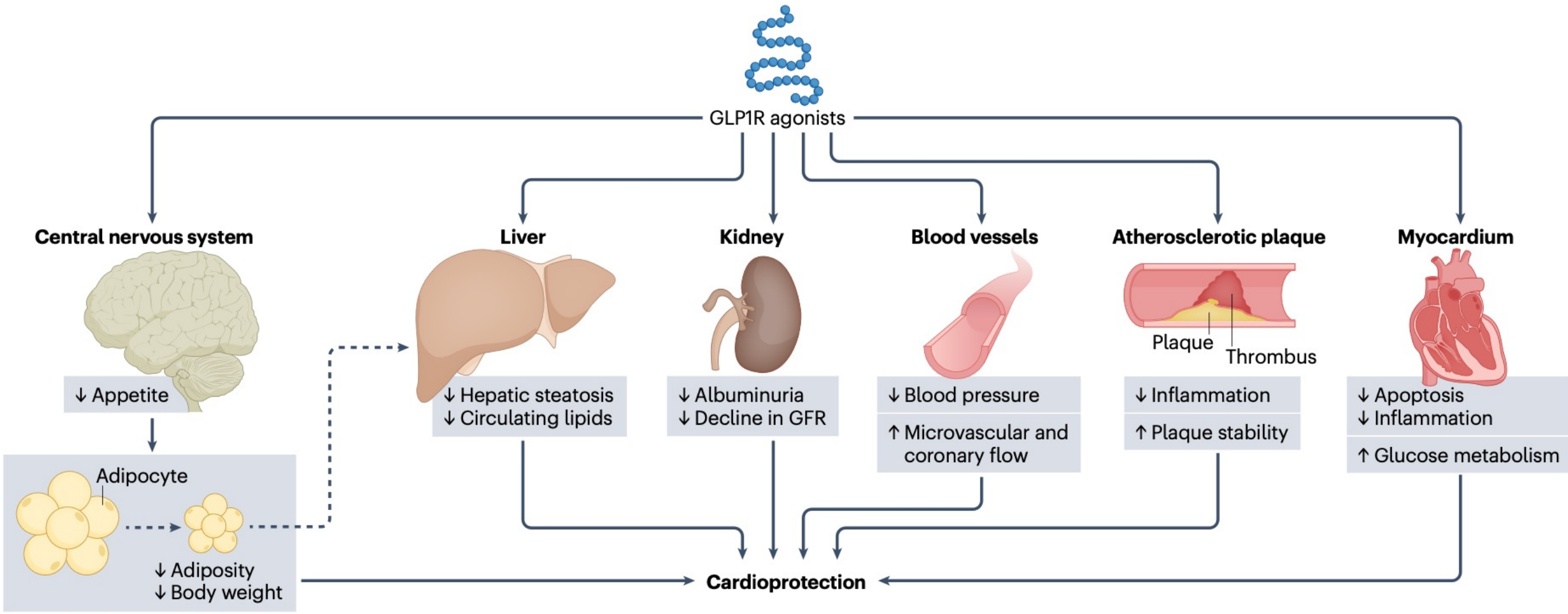


Changes in HbA1c



Wilding et al. Diabetes Obes Metab. 2022;24:1553–1564

Direct and Indirect GLP1RA-Mediated Cardioprotection

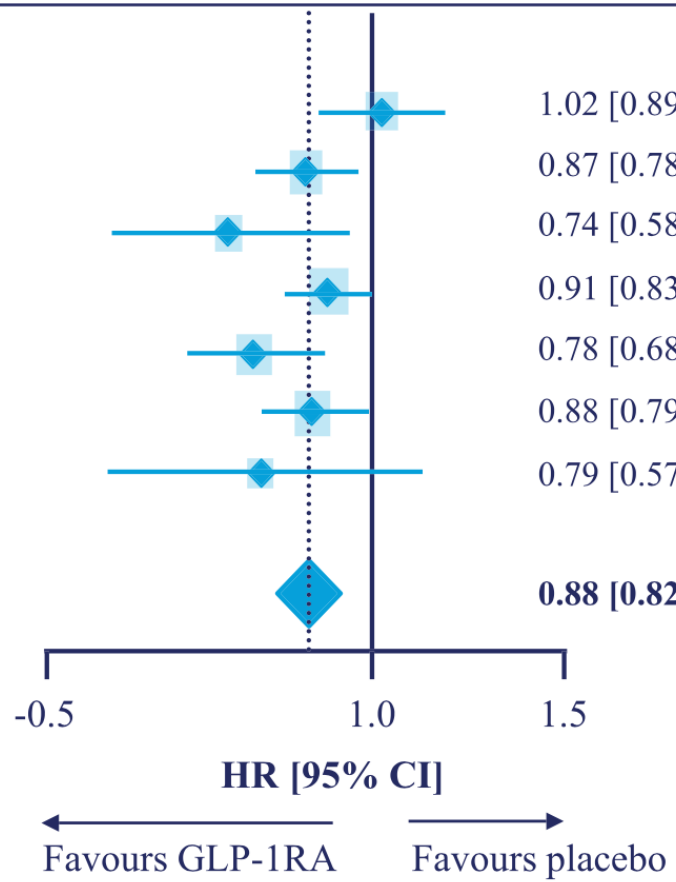


Ussher and Drucker Nat Rev Cardiol 2023 Jul;20(7):463-474

CV Outcome Trials with GLP-1RA in T2DM

	Mean BMI, kg m^{-2} (SD)	GLP-1RA n/N (%)	Placebo n/N (%)	HR [95% CI]	p-value
Three-component MACE					
ELIXA	30.1 (5.6)	400/3,034 (13)	392/3,034 (13)	1.02 [0.89;1.17]	0.78
LEADER	32.5 (6.3)	608/4,668 (13)	694/4,672 (15)	0.87 [0.78;0.97]	0.015
SUSTAIN 6	32.8 (6.2)	108/1,648 (7)	146/1,649 (9)	0.74 [0.58;0.95]	0.016
EXSCEL	32.7 (6.4)	839/7,356 (11)	905/7,396 (12)	0.91 [0.83;1.00]	0.061
HARMONY	32.3 (5.9)	338/4,731 (7)	428/4,732 (9)	0.78 [0.68;0.90]	<0.0001
REWIND	32.3 (5.7)	594/4,949 (12)	663/4,952 (13)	0.88 [0.79;0.99]	0.026
PIONEER 6	32.3 (6.5)	61/1,591 (4)	76/1,592 (5)	0.79 [0.57;1.11]	0.17
OVERALL		**2,948/27,977 (11)**	**3,304/28,027 (12)**	**0.88 [0.82;0.94]**	**<0.0001**

I^2=40.9%, p=0.118

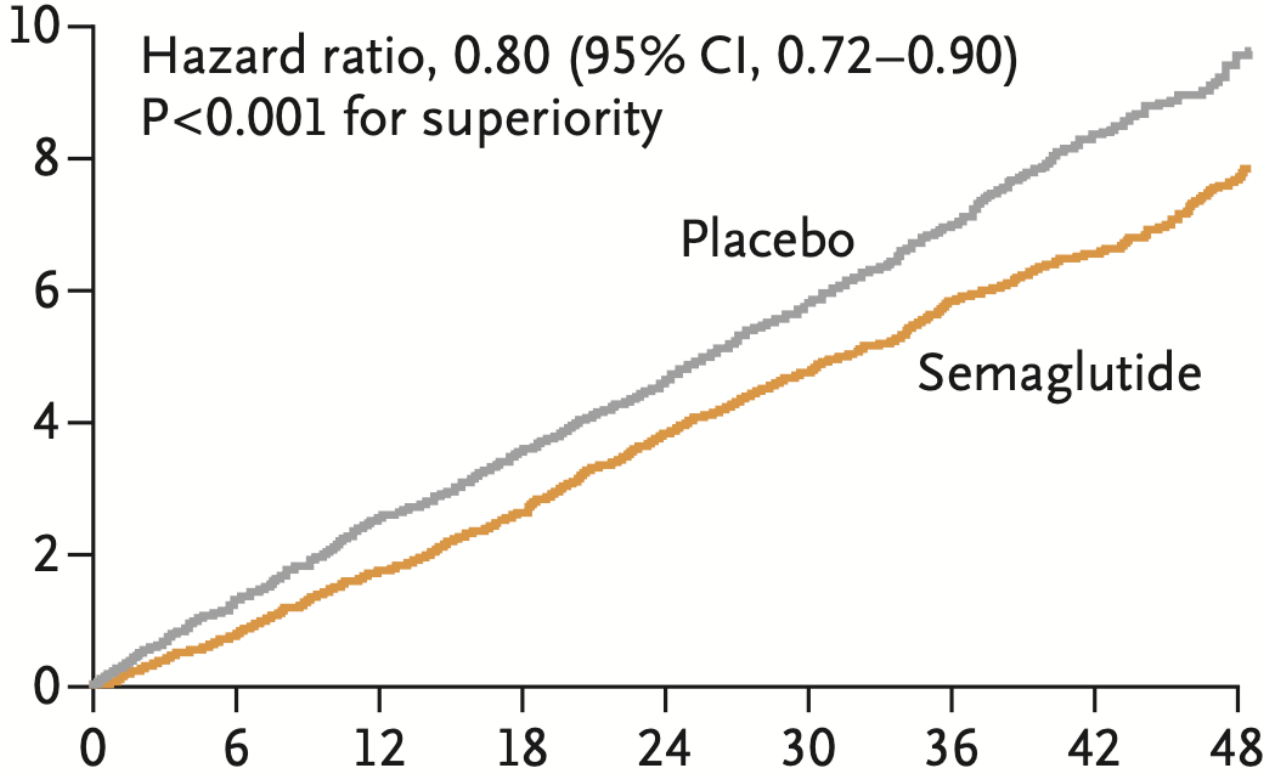


Obesity Reviews 2021;22:e13112

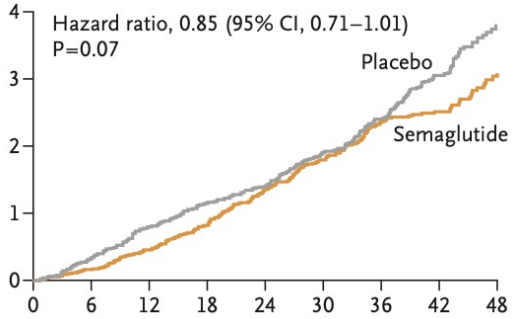
SELECT Trial: Sema 2.4 mg Decreased MACE by 20%

Primary Cardiovascular Composite End Point

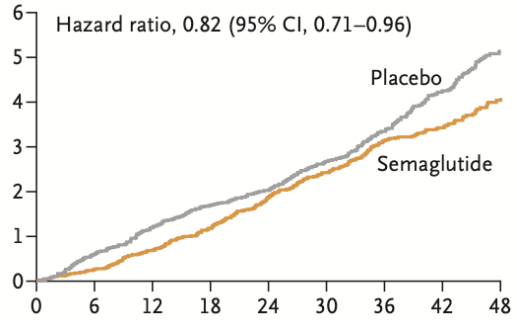
CV death, nonfatal MI, or nonfatal stroke



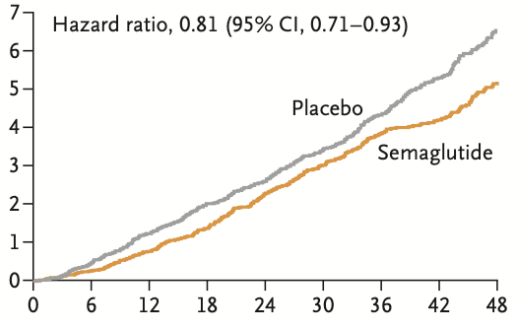
1st Secondary End Point CV Death



2nd Secondary End Point HF Composite



3rd Secondary End Point All Cause Death



Lincoff AM et al. N Engl J Med. 2023 Nov 11. doi: 10.1056/NEJMoa2307563

SELECT Trial Secondary End Points

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

Semaglutide 2.4 mg

Weight -9.4%

WC -8 cm

A1c -0.31%

SBP -3.82 mmHg

DBP -1.0 mmHg

HR 3.8 bpm

hs-CRP -39%

TC -4.6%

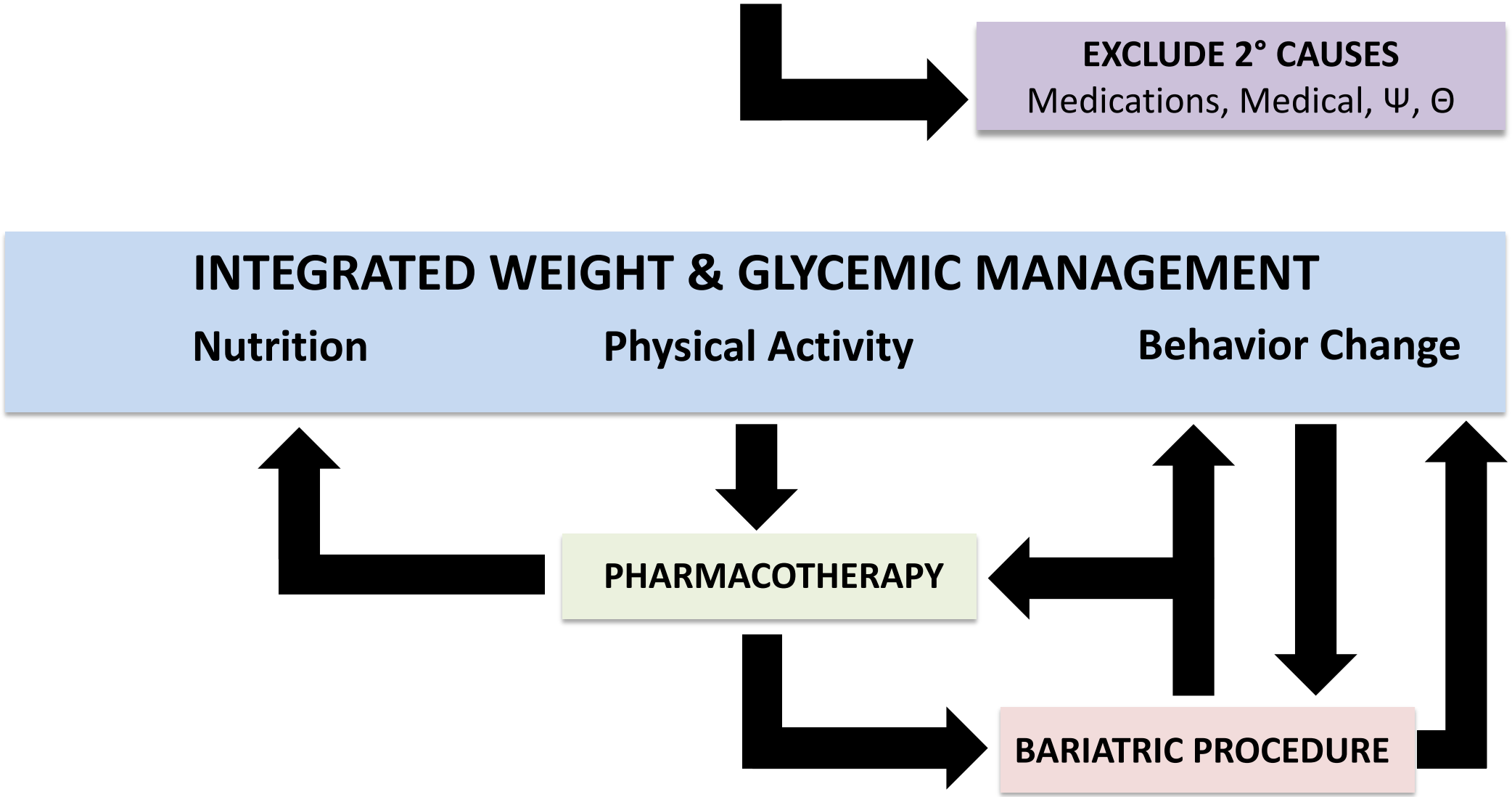
HDL 4.9%

LDL -5.3%

TG -18.3%

Lincoff AM et al. N Engl J Med. 2023 Nov 11. doi: 10.1056/NEJMoa2307563

Treating Obesity as Target in T2D



Case Discussion

Linda Jones
62-year-old accountant recently discharged following NSTEMI and 3 stents to LAD. BMI 42, BP 138/88, HR 64

PMHx
T2D x 9 years (A1c 9.8), HTN, MAFLD, HLD

Current Meds
Metformin 1000 mg twice daily
Glimepiride 4 mg daily
70/30 Insulin 15 units twice daily
Rosuvastatin 20 mg daily
Metoprolol 25 mg twice daily
Losartan 100 mg daily
Clopidogrel 75 mg daily

UT Southwestern
Weight Wellness

Case Discussion

Linda Jones
62-year-old accountant recently discharged following NSTEMI and 3 stents to LAD. BMI 42, BP 138/88, HR 64

PMHx
T2D x 9 years (A1c 9.8), HTN, MAFLD, HLD

Current Meds
Metformin 1000 mg twice daily
~~Glimepiride 4 mg daily~~ **-> Empagliflozin 10 mg daily**
~~70/30 Insulin 15 units~~ **-> Semaglutide 0.25 mg weekly**
Rosuvastatin 20 mg daily
Metoprolol 25 mg twice daily
Losartan 100 mg daily
Clopidogrel 75 mg daily

UT Southwestern
Weight Wellness

Case Discussion

Linda Jones
62-year-old accountant
BMI 42 -> 34, BP 115/74, HR 64

PMHx
T2D x 9 years (A1c 6.8), HTN, MAFLD, HLD

Current Meds
Metformin 1000 mg twice daily
Empagliflozin 10 mg daily
Semaglutide 2.4 mg weekly
Rosuvastatin 20 mg daily
Metoprolol 25 mg twice daily
Losartan 100 mg -> 25 mg daily
Clopidogrel 75 mg daily

UT Southwestern
Weight Wellness

Post-Test Question

Which of the following Food and Drug Administration (FDA) approved anti-obesity medications is associated with the greatest mean weight loss?

a. Phentermine 15 mg daily by mouth
b. Liraglutide 1.8 mg daily by subcutaneous injection
c. Semaglutide 2.4 mg weekly by subcutaneous injection
d. Semaglutide 14 mg daily by mouth
e. Retatrutide 8 mg weekly by mouth

DOS DALLAS OBESITY SOCIETY
ENGAGE ★ EDUCATE ★ EMPOWER

Please answer today's CME questions at menti.com

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UTSouthwestern
Weight Wellness

Post-Test Question

Which of the following Food and Drug Administration (FDA) approved anti-obesity medications is associated with the greatest mean weight loss?

a. Phentermine 15 mg daily by mouth
b. Liraglutide 1.8 mg daily by subcutaneous injection
c. Semaglutide 2.4 mg weekly by subcutaneous injection
d. Semaglutide 14 mg daily by mouth
e. Retatrutide 8 mg weekly by mouth

Answer: c. Semaglutide 2.4 mg weekly by subcutaneous injections is the FDA-approved anti-obesity medication (AOM) in this list with the greatest mean weight reduction. Phentermine 15 mg is the only other FDA-approved AOM in the list and is associated with ~5-8% mean weight loss. Liraglutide 3 mg, and not 1.8 mg, daily is an approved dose for treating obesity. Oral semaglutide 14 mg is approved for treating type 2 diabetes and not obesity. Retatrutide is currently under investigation for treating obesity.

Diabetes and Obesity – Where Do We Fail?

Excess and dysfunctional adiposity is strongly linked to the pathogenesis of T2D. Until recently, glucose has been the primary treatment target

Improvements in glycemia, T2D remission, cardiometabolic outcomes and mortality correlate with weight loss, which is highly variable

Neither AOM nor surgery are curative for T2D or obesity – there are CV and other health benefits that may be independent of weight loss

Advocacy is needed to treat obesity as target in T2D. New incretin therapies and bariatric surgery improve glycemia, weight and CV health

UT Southwestern
Weight Wellness

@JaimeAlmandoz

Thank you!

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Associate Professor of Internal Medicine
Division of Endocrinology and Metabolism
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UT Southwestern
Weight Wellness